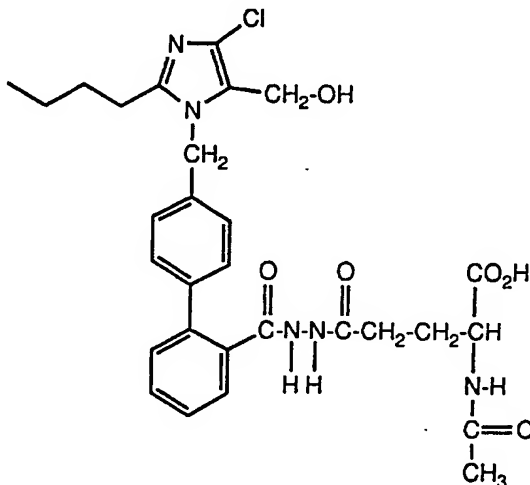




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(54) Title: RENAL-SELECTIVE ANGIOTENSIN II ANTAGONISTS FOR TREATMENT OF HYPERTENSION



(57) Abstract

Renal-selective compounds are described which, in one embodiment, are prodrugs preferentially converted in the kidney to compounds capable of blocking angiotensin II (AII) receptors. These prodrugs are conjugates formed from two components, namely, a first component provided by an AII antagonist compound and a second component which is capable of being cleaved from the first component when both components are chemically linked within the conjugate. The two components are chemically linked by a bond which is cleaved selectively in the kidney, for example, by an enzyme. The liberated AII antagonist compound is then available to block AII receptors within the kidney. Conjugates of particular interest are glutamyl derivatives of biphenylmethyl 1H-substituted imidazole compounds, of which N-acetyl-L-glutamic acid, 5-[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl] [1,1'-biphenyl]-2-yl]carbonylhydrazone shown above is an example.

+ DESIGNATIONS OF "SU"

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**RENAL-SELECTIVE ANGIOTENSIN II ANTAGONISTS FOR
TREATMENT OF HYPERTENSION**

Field of the Invention

5

This invention is in the field of cardiovascular therapeutics and relates to a class of compounds useful in control of hypertension. Of particular interest is a class of prodrugs of angiotensin II antagonists which, when selectively
10 hydrolyzed in the kidney, provide hypertension control.

Background of the Invention

The renin-angiotensin system is one of the hormonal
15 mechanisms involved in regulation of pressure/volume homeostasis and in expression of hypertension. Activation of the renin-angiotensin cascade begins with renin secretion from the juxtaglomerular apparatus of the kidney and culminates in the formation of angiotensin II, an octapeptide which is the
20 primary active species of this system. Angiotensin II is a potent vasoconstrictor agent and also produces other physiological effects such as promoting aldosterone secretion, promoting sodium and fluid retention, inhibiting renin secretion, increasing sympathetic nervous system activity,
25 increasing vasopressin secretion, causing positive cardiac inotropic effect and modulating other hormonal systems.

Previous studies have shown that antagonizing angiotensin II at its receptors is a viable approach to
30 inhibit the renin-angiotensin system, given the pivotal role of this octapeptide which mediates the actions of the renin-angiotensin system through interaction with various tissue receptors. There are several known angiotensin II antagonists, most of which are peptidic in nature. Such
35 peptidic compounds are of limited use due to their lack of

oral bioavailability or their short duration of action. Also, commercially-available peptidic angiotensin II antagonists (e.g., Saralasin) have a significant residual agonist activity which further limit their therapeutic application.

5

Non-peptidic compounds with angiotensin II antagonist properties are known. For example, the sodium salt of 2-n-butyl-4-chloro-1-(2-chlorobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [P. C. Wong et al, J. Pharmacol. Exp. Ther., 247 (1), 1-7 (1988)]. Also, the sodium salt of 2-butyl-4-chloro-1-(2-nitrobenzyl)imidazole-5-acetic acid has specific competitive angiotensin II antagonist activity as shown in a series of binding experiments, functional assays and in vivo tests [A. T. Chiu et al, European J. Pharmacol., 157, 3121 (1988)]. A family of 1-benzylimidazole-5-acetate derivatives has been shown to have competitive angiotensin II antagonist properties [A. T. Chiu et al, J. Pharmacol. Exp. Ther., 250 (3), 867-874 (1989)]. U.S. Patent No. 4,816,463 to Blankey et al describes a family of 4,5,6,7-tetrahydro-1H-imidazo(4,5-c)-tetrahydro-pyridine derivatives useful as antihypertensives, some of which are reported to antagonize the binding of labelled angiotensin II to rat adrenal receptor preparation and thus cause a significant decrease in mean arterial blood pressure in conscious hypertensive rats. EP No. 253,310, published 20 January 1988, describes a series of aralkyl imidazole compounds, including in particular a family of biphenylmethyl substituted imidazoles, as antagonists to the angiotensin II receptor. EP No. 323,841 published 12 July 1989 describes four classes of angiotensin II antagonists, namely, biphenylmethylpyrroles, biphenylmethylpyrazoles, biphenylmethyl-1,2,3-triazoles and biphenylmethyl 4-substituted-4H-1,2,4-triazoles, including the compound 3,5-

dibutyl-4-[(2'-carboxybiphenyl-4-yl)methyl]-4H-1,2,4-triazole.
U.S. Patent No. 4,880,804 to Carini et al describes a family
of biphenylmethylbenzimidazole compounds as angiotensin II
receptor blockers for use in treatment of hypertension and
5 congestive heart failure.

One disadvantage of these angiotensin II antagonist
compounds is that the desired hypertension-reducing effect may
be offset by hypotension-induced compensatory stimulation of
10 the renin-angiotensin system or stimulation of the sympathetic
nervous system, either of which may result in promotion of
sodium and water retention. Also, some angiotensin II
antagonists may have toxicological effects systemically which
precludes their use at doses necessary to be effective in
15 reducing blood pressure.

To avoid such systemic side effects, drugs may be
targetted to the kidney by creating a conjugate compound that
would be a renal-specific prodrug containing the targetted
20 drug modified with a chemical carrier moiety. Cleavage of the
drug from the carrier moiety by enzymes predominantly
localized in the kidney releases the drug in the kidney. Gamma
glutamyl transpeptidase and acylase are examples of such
cleaving enzymes found in the kidney which have been used to
25 cleave a targetted drug from its prodrug carrier within the
kidney.

Renal targetted prodrugs are known for delivery of
a drug selectively to the kidney. For example, the compound L-
30 γ -glutamyl amide of dopamine when administered to dogs was
reported to generate dopamine in vivo by specific enzymatic
cleavage by γ -glutamyl transpeptidase [J. J. Kyncl et al, Adv.
Biosc., 20, 369-380 (1979)]. In another study, γ -glutamyl and
N-acyl- γ -glutamyl derivatives of the anti-bacterial compound
35 sulfamethoxazole were shown to deliver relatively high

concentrations of sulfamethoxazole to the kidney which involved enzymatic cleavage of the prodrug by acylamino acid deacylase and γ -glutamyl transpeptidase [M. Orłowski et al, J. Pharmacol. Exp. Ther., 212, 167-172 (1980)]. The N- γ -glutamyl derivatives of 2-, 3-, or 4-aminophenol and p-fluoro-L-phenylalanine have been found to be readily solvolyzed in vitro by γ -glutamyl transpeptidase [S.D.J. Magnan et al, J. Med. Chem., 25, 1018-1021 (1982)]. The hydralazine-like vasodilator 2-hydrazino-5-n-butylpyridine (which stimulates guanylate cyclase activity) when substituted with the N-acetyl- γ -glutamyl residue resulted in a prodrug which provided selective renal vasodilation [K. G. Hofbauer et al, J. Pharmacol. Exp. Ther., 212, 838-844 (1985)]. The dopamine prodrug γ -L-glutamyl-L-dopa ("gludopa") has been shown to be relatively specific for the kidney and to increase renal blood flow, glomerular filtration and urinary sodium excretion in normal subjects [D. P. Worth et al, Clin. Sci., 69, 207-214 (1985)]. In another study, gludopa was reported to be an effective renal dopamine prodrug whose activity can be blocked by the dopa-decarboxylase inhibitor carbidopa [R. F. Jeffrey et al, Br. J. Clin. Pharmacol., 25, 195-201 (1988)]. A class of 4-ureido derivatives of isoquinolin-3-ol has been investigated for renal specific effects such as increases in renal vasodilation and renal blood flow [R. M. Kanojia et al, J. Med. Chem., 32, 990-997 (1989)].

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Fig. 1 is a graph showing reduction in mean arterial pressure by intravenous administration of a conjugate of the invention to a spontaneously hypertensive rat.

Fig. 2 is a graph showing angiotensin II pressor response in a spontaneously hypertensive rat infused by

intravenous administration with a conjugate of the invention over a period of three days.

Fig. 3 is a graph showing urinary sodium excretion response to angiotensin II infusion in conscious normotensive rats followed by administration of a saline vehicle, an angiotensin II antagonist, or a renal-selective conjugate of the invention.

Fig. 4 is a graph showing mean arterial pressure response to angiotensin II infusion in conscious normotensive rats followed by administration of a saline vehicle, an angiotensin II antagonist, or a renal-selective conjugate of the invention..

DESCRIPTION OF THE INVENTION

Treatment of chronic hypertension or sodium-retaining disorders such as congestive heart failure, cirrhosis and nephrosis, may be accomplished by administering to a susceptible or afflicted subject a therapeutically-effective amount of a renal-selective prodrug capable of causing blood-pressure reducing effects by selective action in the kidney. An advantage of such renal-selective prodrug therapy resides in reduction or avoidance of adverse side effects associated with systemically-acting drugs.

Advantages of a renal-selective antihypertensive compound are several. First, the renal-selective compound is targetted at those pathophysiological mechanisms which occur primarily in the kidney. Second, the regulation of other organ systems is unaffected; thus, normal physiological regulation of other organ systems is maintained. Third, fewer side-effects may be anticipated, since the compound remains

inactive until cleaved in the kidneys. Similarly, fewer negative drug-drug interactions may be anticipated. Finally, since a renal-selective accumulation of active compound may occur, which is not dependent on plasma levels of the parent
5 compound, lower doses of the renal-selective compound compared to active parent compound may be used.

A renal-selective prodrug is provided by a conjugate comprising a residue of an angiotensin II antagonist
10 compound, which conjugate is renal selective. The conjugate will typically comprise a first component and a second component connected together by a cleavable or hydrolyzable bond. The term "renal-selective", as used to characterize a conjugate of the invention, embraces any of the following four
15 pharmacological events: (1) the conjugate is selectively taken up by the kidney and is selectively cleaved in the kidney; (2) the conjugate is not taken up selectively by the kidney, but is selectively cleaved in the kidney; (3) the conjugate is selectively taken up by the kidney and then
20 cleaved in the kidney; or (4) where the conjugate itself is active as an angiotensin II antagonist, the conjugate is selectively taken up by the kidney without cleavage of the hydrolyzable bond.

25 The first component of a conjugate of the invention is a residue derived from an antagonist compound capable of inhibiting angiotensin II (AII) receptors, especially those AII receptors located in the kidney. The second residue is capable of being cleaved from the first residue
30 preferentially. Cleaving of the first and second residues may be accomplished by a variety of mechanisms. For example, the bond may be cleaved by an enzyme in the kidney.

The residue providing the first component may be
35 characterized as the "AII antagonist active" residue. Such

"active" residue may be provided by a compound having AII antagonist activity or by a metabolite of such compound having AII antagonist activity. The residue providing the second component may be characterized in being capable of forming a cleavable bond connecting the "active" first residue and the second residue. Such bond is cleavable by an enzyme located in the kidney. In a preferred embodiment, this cleavable bond is typically a hydrolyzable amide bond, that is, a bond between a carbonyl-terminated moiety and a reactive nitrogen-terminated moiety, such as an amino-terminated moiety, which may be cleaved by an enzyme found in the kidney, but which is not cleaved substantially by enzymes located in other organs or tissues of the body. Preferred bond-cleaving enzymes would be found predominantly in the kidney.

The conjugate containing the residue of an AII antagonist compound and containing the cleavable fragment or residue may possess AII antagonist activity comparable to, or more than, or less than, the AII antagonist compound which forms the conjugate. In one embodiment of the invention, the conjugate will have AII receptor blocking activity comparable to the AII antagonist component forming the conjugate. In another embodiment of the invention, the conjugate will have AII receptor blocking activity less than the AII receptor blocking activity forming the conjugate. One advantage of such differential activity between the conjugate and the AII antagonist component is that certain side effects associated with non-renal, systemic AII receptor blocking may be avoided or reduced. For example, at least one conjugate of the invention has been found to have a very large differential in AII receptor blocking activities between the conjugate and the AII antagonist component forming the conjugate. Such differential activity is advantageous in that therapeutically-effective antihypertensive doses of the conjugate may be administered to give renal-selective AII receptor blocking

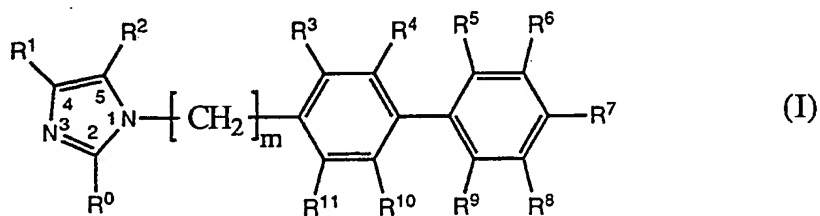
action resulting from kidney-specific enzyme hydrolysis or metabolism of the conjugate to free the active AII receptor blocker within the kidney. Inasmuch as this renal-selective conjugate has relatively low AII receptor blocking activity, compared to the AII receptor compound forming the conjugate, this conjugate will have fewer adverse side effects associated with unwanted systemic interaction with non-renal AII receptors such as found in the vascular bed.

10

DETAILED DESCRIPTION OF THE INVENTION

The first residue of the conjugate may be selected from any class of compounds, or metabolites thereof, having angiotensin II antagonist activity. An example of one such class of angiotensin II antagonist compounds is provided by a class of biphenylmethyl 1H-substituted-1,3-imidazole compounds defined by Formula I:

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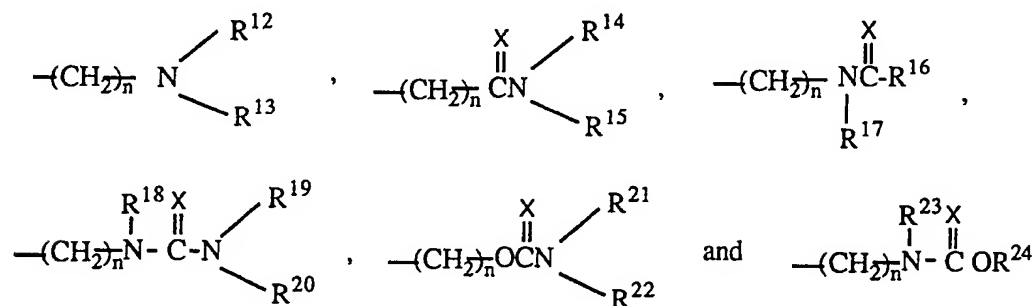


wherein m is a number selected from one to four, inclusive;

wherein each of R⁰ through R¹¹ is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl,

mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl,
 alkoxycarbonyloxy, alkylthio, cycloalkylthio,
 alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy,
 alkylthiocarbonylthio, alkylthiothiocarbonyl,
 5 alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl,
 arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio,
 arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio,
 aralkylthiocarbonyl, aralkylcarbonylthio,
 aralkylthiocarbonyloxy, aralkylthiocarbonylthio,
 10 alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto,
 alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl,
 aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido,
 phthalimidoalkyl, heteroaryl, heteroarylalkyl,
 cycloheteroalkyl, cycloheteroalkylalkyl and
 15 cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl-
 and cyclohetero-containing groups has one or more ring atoms
 selected from oxygen, sulfur and nitrogen atoms, and wherein
 each of R^0 through R^{11} may be further independently selected
 from amino and amido radicals of the formula

20



wherein X is oxygen atom or sulfur atom;

25

wherein each n is a number independently selected from zero to
 six, inclusive;

wherein each of R¹² through R²⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R¹² and R¹³ taken together, R¹⁴ and R¹⁵ taken together, R¹⁶ and R¹⁷ taken together, R¹⁹ and R²⁰ taken together and R²¹ and R²² taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R¹² and R¹³ taken together, R¹⁴ and R¹⁵ taken together, R¹⁹ and R²⁰ taken together and R²¹ and R²² taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

and wherein each of R³ through R¹¹ may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

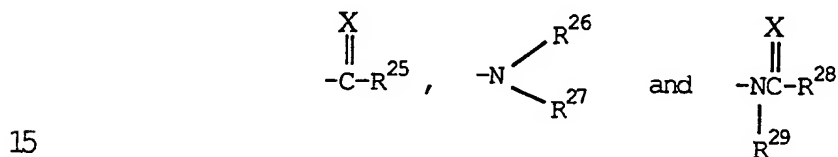


wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties;

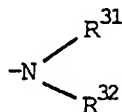
wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing R¹ through R²⁴, Y and A

groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxy carbonyloxy, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula

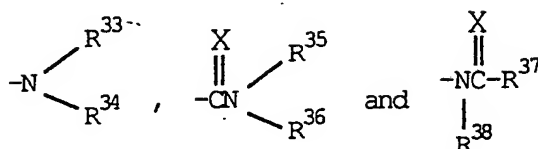


wherein X is selected from oxygen atom and sulfur atom; wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR³⁰ and



wherein D is selected from oxygen atom and sulfur atom and R³⁰ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is further

independently selected from amino and amido radicals of the formula



5

wherein X is oxygen atom or sulfur atom;

wherein each of R³³, R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R²⁶ and R²⁷ taken together and R²⁸ and R²⁹ taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R²⁶ and R²⁷ taken together and R³¹ and R³² taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

25

with the proviso that at least one of said R¹ through R²⁴, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

30

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

Conjugates of the invention are therapeutically effective in treatment of cardiovascular disorders by acting directly, or by providing cleavable components selected from Formula I compounds which act directly, as antagonists to, or blockers of, the angiotensin II (AII) receptor. Thus, conjugates of Formula I would be therapeutically effective in treatment of cardiovascular disorders or would be precursors to, or prodrugs of, therapeutically-effective compounds.

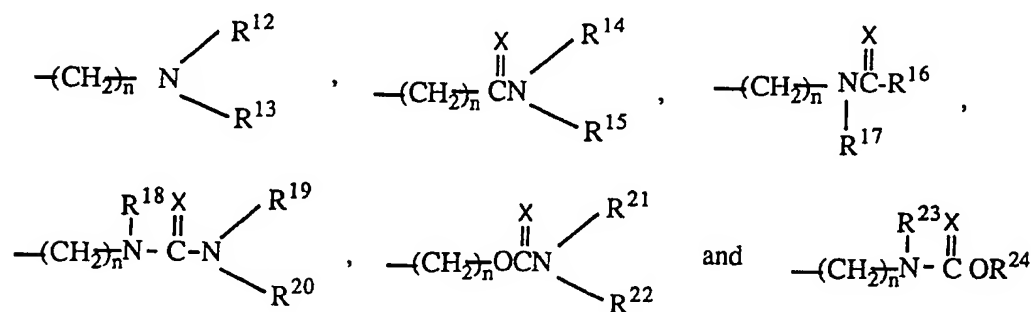
Preferred compounds of Formula I, from which a cleavable component may be selected, are all characterized in having a substituent, other than hydrido, at each of the four- and five-positions of the imidazole ring. Such substituents are selected from the aforementioned R^1 and R^2 groups.

The phrase "acidic group selected to contain at least one acidic hydrogen atom", as used to define the $-Y_nA$ moiety, is intended to embrace chemical groups which, when attached to any of the R^3 through R^{11} positions of Formula I, confers acidic character to the compound of Formula I. "Acidic character" means proton-donor capability, that is, the capacity of the compound of Formula I to be a proton donor in the presence of a proton-receiving substance such as water. Typically, the acidic group should be selected to have proton-donor capability such that the product compound of Formula I has a pK_a in a range from about one to about twelve. More typically, the Formula I compound would have a pK_a in a range from about two to about seven. An example of an acidic group containing at least one acidic hydrogen atom is carboxyl group ($-COOH$). Where n is zero and A is $-COOH$, in the $-Y_nA$ moiety, such carboxyl group would be attached directly to one of the R^3 through R^{11} positions. The Formula I compound may have one

-Y_nA moiety attached at one of the R³ through R¹¹ positions, or may have a plurality of such -Y_nA moieties attached at more than one of the R³ through R¹¹ positions, up to a maximum of nine such -Y_nA moieties. There are many examples of acidic groups other than carboxyl group, selectable to contain at least one acidic hydrogen atom. Such other acidic groups may be collectively referred to as "bioisosteres of carboxylic acid" or referred to as "acidic bioisosteres". Specific examples of such acidic bioisosteres are described hereinafter. Compounds of Formula I having the -Y_nA moiety attached at one of positions R⁵, R⁶, R⁸ and R⁹ would be expected to have preferred properties, while attachment at R⁵ or R⁹ would be more preferred.

A preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R⁰ through R¹¹ is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxy carbonylalkyl, aralkoxy carbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxy carbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto,

- alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and
- 5 cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R⁰ through R¹¹ may be further independently selected from amino and amido radicals
- 10 of the formula



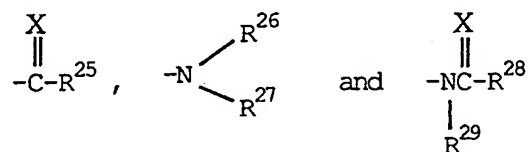
- 15 wherein X is selected from oxygen atom or sulfur atom;
- wherein each n is a number independently selected from zero to six, inclusive;
- 20 wherein each of R¹² through R²⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;
- 25 and wherein each of R³ through R¹¹ may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula



wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

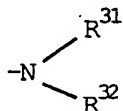
and wherein any of the foregoing R¹ through R²⁴, Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula

20



wherein X is selected from oxygen atom and sulfur atom; wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR³⁰ and

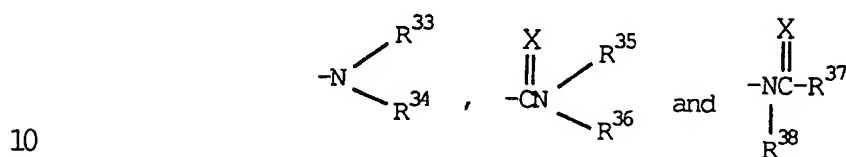
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wherein D is selected from oxygen atom and sulfur atom, and R³⁰ is selected from hydrido, alkyl, cycloalkyl,

30

cycloalkylalkyl, aralkyl and aryl; wherein each of R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

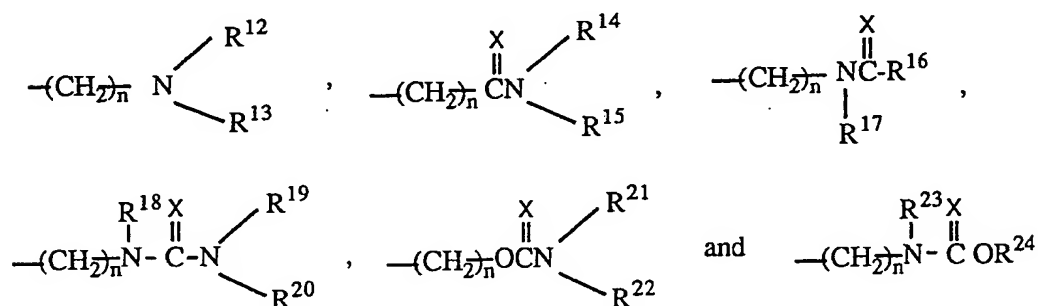
15 wherein each of R²⁶ through R³¹ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

20 with the proviso that at least one of said R¹ through R²⁴, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

25 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

30 A more preferred class of compounds within the subclass defined by Formula I consists of those compounds wherein m is one; wherein each of R⁰ through R¹¹ is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl,

- alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl,
- 5 aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and
- 10 cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals
- 15 of the formula



- 20 wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

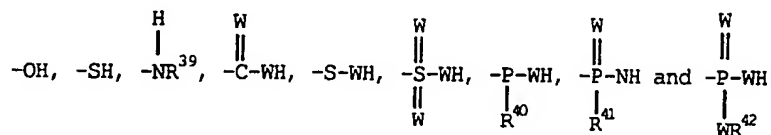
- 25 wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

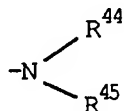


wherein n is a number selected from zero through three, inclusive;

- 10 wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



- 15 wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43} ; wherein each of R^{39} , R^{40} , R^{41} , R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} , R^{40} , R^{41} and R^{42} may be further independently selected from amino radicals of the formula



- 25 wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom
- 30 of said amino radical, which heterocyclic group may further

contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R⁴⁴ and R⁴⁵ taken together may form an aromatic heterocyclic group having
5 five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R⁴⁰ and R⁴¹ may be further independently selected from hydroxy, alkoxy,
10 alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

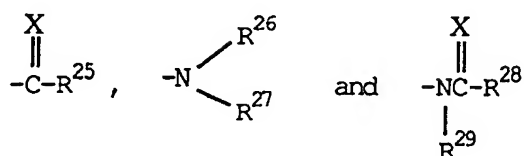
wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of
15 heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a
20 single position selected from R³ through R¹¹ or may be attached at any two adjacent positions selected from R³ through R¹¹ so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic
25 groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

30 and wherein any of the foregoing R¹ through R²⁴, Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy,
35 aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxyalkyl,

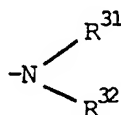
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carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



5

wherein X is selected from oxygen atom and sulfur atom;
wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR³⁰ and



10

wherein D is selected from oxygen atom and sulfur atom,
wherein R³⁰ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

15

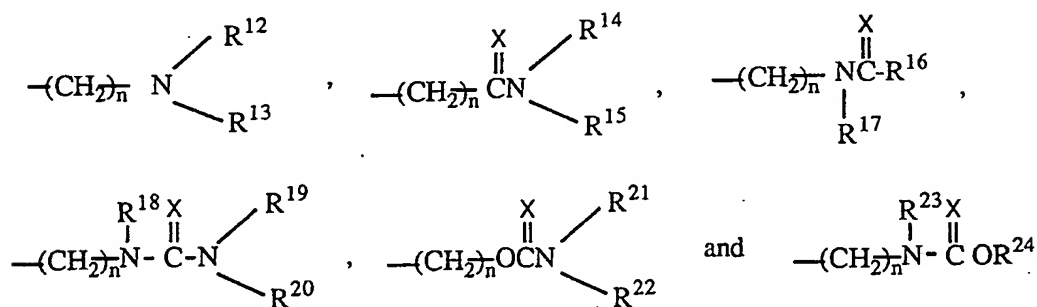
wherein each of R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is
independently selected from hydrido, alkyl, cycloalkyl, cyano,
hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl,
alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl,
20 haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R¹ through R²⁴, Y
and A substituents contains a terminal primary or secondary
amino moiety or a moiety convertible to a primary or secondary
25 amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

SUBSTITUTE SHEET

An even more preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R⁰, R¹ and R² is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxy carbonylalkyl, aralkoxy carbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxy carbonyloxy, alkylthio, cycloalkylthio, arylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R⁰ through R¹¹ may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

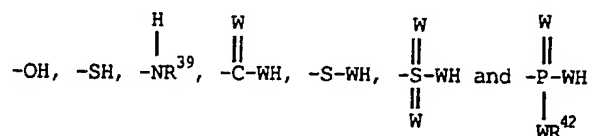
5 wherein each of R¹² through R²⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

10 wherein each of R³ through R¹¹ is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, 15 alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

20 and wherein each of R³ through R¹¹ may be an acidic moiety further independently selected from acidic moieties of the formula

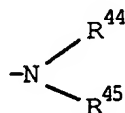


25 wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



30 wherein each W is independently selected from oxygen atom, sulfur atom and NR⁴³; wherein each of R³⁹, R⁴² and R⁴³ is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl,

cycloalkylalkyl, aryl and aralkyl; wherein each of R³⁹ and R⁴² may be further independently selected from amino radical of the formula



5

wherein each of R⁴⁴ and R⁴⁵ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein
10 R⁴⁴ and R⁴⁵ taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic
15 group may be saturated or partially unsaturated; wherein R⁴⁴ and R⁴⁵ taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms
20 selected from oxygen, nitrogen and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which
25 ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R³ through R¹¹ or may be attached at any two
30 adjacent positions selected from R³ through R¹¹ so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

5

wherein each of R¹ through R²⁴, Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

10

with the proviso that at least one of said R¹ through R²⁴, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

15

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

20

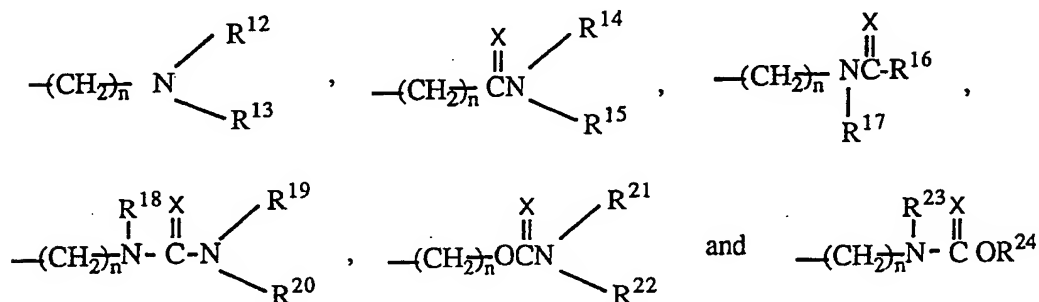
A highly preferred class of compounds within the sub-class defined by Formula I consists of those compounds wherein m is one; wherein each of R⁰, R¹ and R² is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl-

25

30

35

- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



- 10 wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

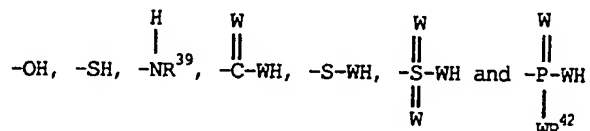
- 15 wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

- 20 wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

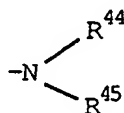
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula



wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



10 wherein each W is independently selected from oxygen atom, sulfur atom and NR⁴³; wherein each of R³⁹, R⁴² and R⁴³ is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R³⁹ and R⁴² may be further independently selected from amino radical of the formula



wherein each of R⁴⁴ and R⁴⁵ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, 20 alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form

a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

5 wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

10 wherein each of R^1 through R^{24} , Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

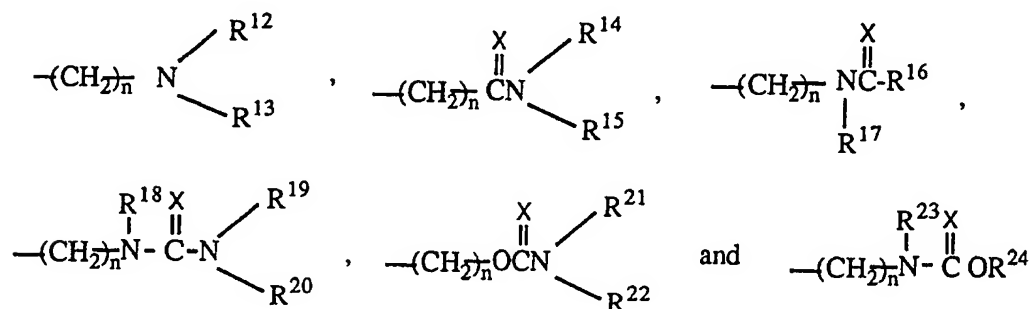
15 with the proviso that at least one of said R^1 through R^{24} , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

20 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

An even more highly preferred class of compounds
25 within Formula I consists of those compounds wherein m is one; wherein R^0 is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of R^1 and R^2 is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl,
30 alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl,
35 alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl,

aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula

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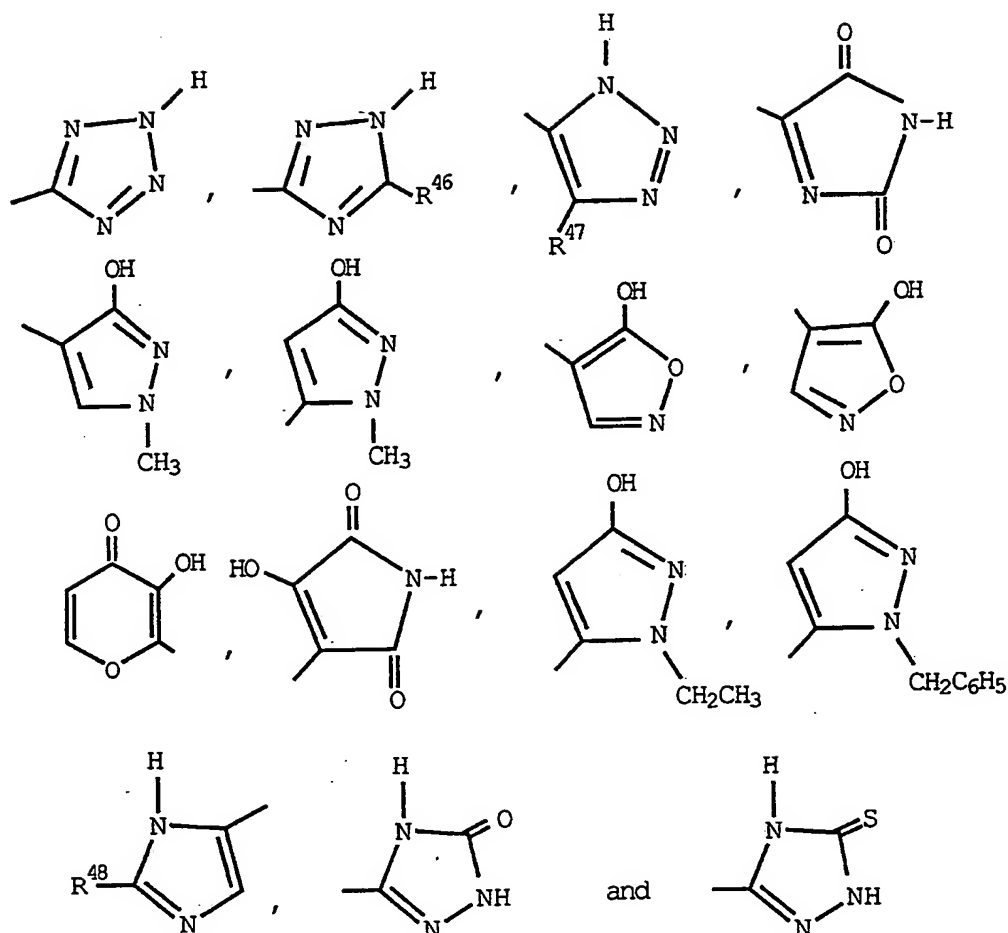
10 wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

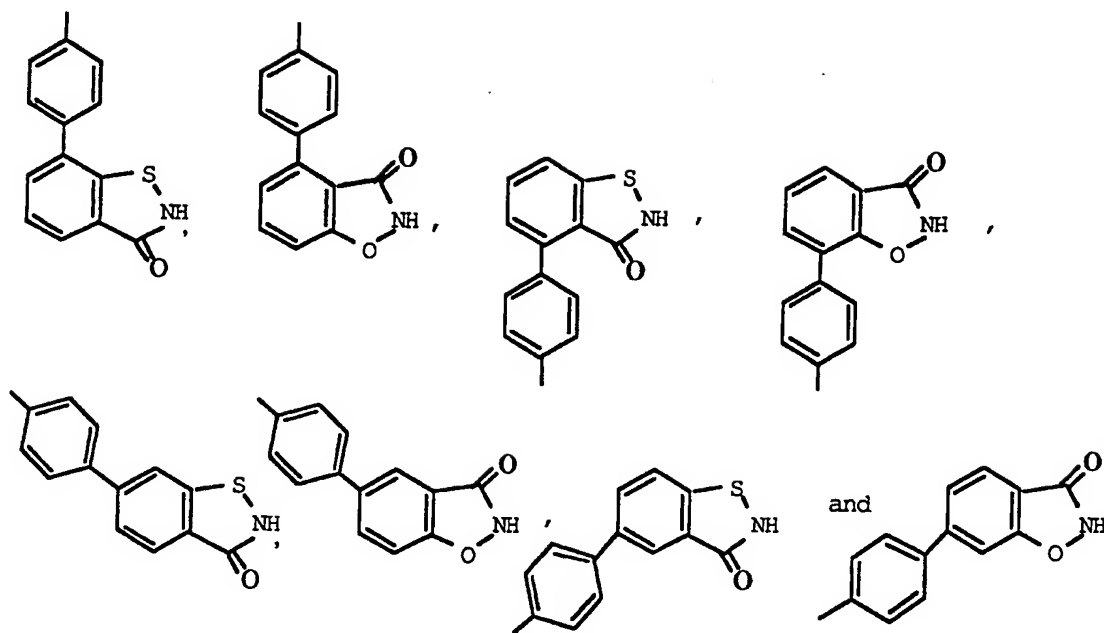
15 wherein each of R¹² through R²⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

20 wherein each of R³ through R¹¹ is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

25 and wherein each of R³ through R¹¹ may be an acidic moiety further independently selected from acidic moieties consisting of CO₂H, CO₂CH₃, SH, CH₂SH, C₂H₄SH, PO₃H₂, NHSO₂CF₃, NHSO₂C₆F₅, SO₃H, CONHNH₂, CONHNHSO₂CF₃, CONHOCH₃, CONHOC₂H₅, CONHCF₃, OH, CH₂OH, C₂H₄OH, OPO₃H₂, OSO₃H,






- wherein each of R⁴⁶, R⁴⁷ and R⁴⁸ is independently selected from H, Cl, CN, NO₂, CF₃, C₂F₅, C₃F₇, CHF₂, CH₂F, CO₂CH₃, CO₂C₂H₅, SO₂CH₃, SO₂CF₃ and SO₂C₆F₅; wherein Z is selected from O, S, NR⁴⁹ and CH₂; wherein R⁴⁹ is selected from hydrido, CH₃ and CH₂C₆H₅; and wherein said acidic moiety may be a heterocyclic acidic group attached at any two adjacent positions of R³ through R¹¹ so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I; said biphenyl fused ring system selected from



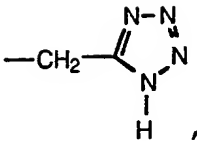




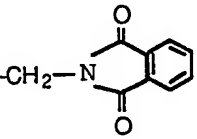

and the esters, amides and salts of said acidic moieties;

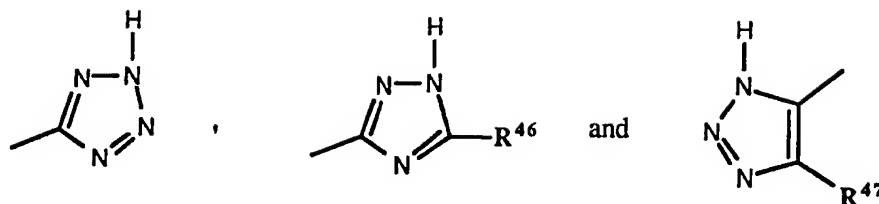
- 5 with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A class of compounds of particular interest within Formula I consists of those compounds wherein m is one;

15 wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH=CH$, $C_3H_7(n)$, SC_3H_7 ,  CH_2 , , C_2H_5 , $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9 ,  CH_2S , $CH_3CH=CH$ and $CH_3CH_2CH_2CH=CH$ -; wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH , CH_2OCOCH_3 , CH_2Cl , Cl , CH_2OCH_3 , $CH_2OCH(CH_3)_2$, I , CHO ,

20

- $\text{CH}_2\text{CO}_2\text{H}$, $\text{CH}(\text{CH}_3)\text{CO}_2\text{H}$, NO_2 , Cl ,
,
 $-\text{CH}_2\text{OCOCH}_2\text{CH}_2-$ , $-\text{CO}_2\text{CH}_3$, $-\text{CONH}_2$, $-\text{CONHCH}_3$, $\text{CON}(\text{CH}_3)_2$,
 $-\text{CH}_2-\text{NHCO}_2\text{C}_2\text{H}_5$, $-\text{CH}_2\text{NHCO}_2-$ , $-\text{CH}_2\text{NHCO}_2\text{CH}_3$, $-\text{CH}_2\text{NHCO}_2\text{C}_3\text{H}_7$,
 $-\text{CH}_2\text{NHCO}_2\text{CH}_2(\text{CH}_3)_2$, $-\text{CH}_2\text{NHCO}_2\text{C}_4\text{H}_9$, CH_2NHCO_2 -adamantyl,
5 $-\text{CH}_2\text{NHCO}_2$ -(1-naphthyl), $-\text{CH}_2\text{NHCONHCH}_3$, $-\text{CH}_2\text{NHCONHC}_2\text{H}_5$,
 $-\text{CH}_2\text{NHCONHC}_3\text{H}_7$, $-\text{CH}_2\text{NHCONHC}_4\text{H}_9$, $-\text{CH}_2\text{NHCONHCH}(\text{CH}_3)_2$,
 $-\text{CH}_2\text{NHCONH}$ (1-naphthyl), $-\text{CH}_2\text{NHCONH}$ (1-adamantyl), CO_2H ,
 $-\text{CH}_2\text{CH}_2\text{CO}-\text{N}$ , $-\text{CH}_2\text{CH}_2\text{CO}-\text{N}$ , $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$,
 $-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{OCONHCH}_3$, $-\text{CH}_2\text{OCSNHCH}_3$, $-\text{CH}_2\text{NHC}_3\text{H}_7\text{S}$,
10 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{ONO}_2$,
, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{O}-$ ,
 H , Cl , NO_2 , CF_3 , CH_2OH , Br , F , I , methyl, ethyl, n-propyl,
isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl,
isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl,
cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-
15 oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-
dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-
difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-
difluoropentyl; wherein each of R^3 through R^{11} is hydrido, with
the proviso that at least one of R^5 , R^6 , R^8 and R^9 is an
20 acidic group selected from CO_2H , SH , PO_3H_2 , SO_3H , CONHNH_2 ,
 $\text{CONHNHSO}_2\text{CF}_3$, OH ,



wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

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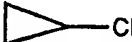
with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

10


or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

15 A class of compounds of more particular interest within Formula I consists of those compounds wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH=CH$, $C_3H_7(n)$,

SC_3H_7 , , , C_2H_5 , $C_5H_{11}(n)$, $C_6H_{13}(n)$,

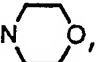
SC_4H_9 , , $CH_3CH=CH$ and $CH_3CH_2CH_2CH=CH-$; wherein R^1

20 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH , CH_2OCOCH_3 , CH_2Cl , Cl, CH_2OCH_3 , $CH_2OCH(CH_3)_2$, I, CHO, CH_2CO_2H , $CH(CH_3)CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$, -

$CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2-$ , $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, -

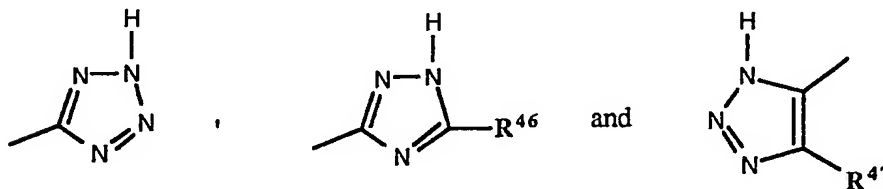
$CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2 -adamantyl, -
 CH_2NHCO_2 -(1-naphthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, -

25 $CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, -
 $CH_2NHCONH$ (1-naphthyl), $-CH_2NHCONH$ (1-adamantyl), CO_2H ,

$-CH_2CH_2-CO-N$ , $-CH_2CH_2CH_2CO_2H$,

$-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{OCONHCH}_3$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{SH}$ and $-\text{CH}_2\text{O}-\text{C}_6\text{H}_5$;

wherein R^2 is selected from H, Cl, NO_2 , CF_3 , CH_2OH , Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R^3 through R^{11} is hydrido, with the proviso that at least one of R^5 , R^6 , R^8 and R^9 is an acidic group selected from CO_2H , SH, PO_3H_2 , SO_3H , CONHNH_2 , $\text{CONHNHSO}_2\text{CF}_3$, OH,









wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

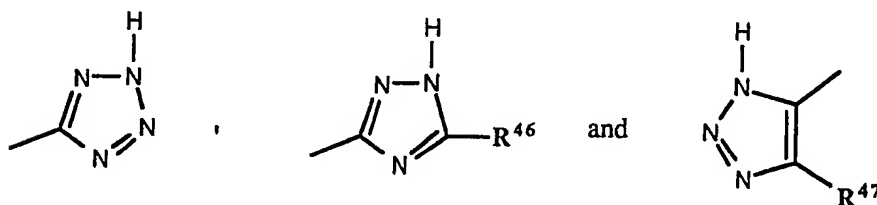
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

A class of compounds of even more particular interest within Formula I consists of those compounds wherein m is one; wherein R^0 is selected from $\text{C}_4\text{H}_9(\text{n})$, $\text{CH}_3\text{CH}_2\text{CH}=\text{CH}$,

- $C_3H_7(N)$, SC_3H_7 , , , C_2H_5 , $C_5H_{11}(n)$,
 $C_6H_{13}(n)$, SC_4H_9 , , $CH_3CH=CH$ and $CH_3CH_2CH_2CH=CH-$;
 wherein R^1 is selected from H, Cl, NO_2 , CF_3 , CH_2OH , Br, F, I,
 methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl,
 5 isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl,
 benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl,
 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl,
 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo,
 difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-
 10 difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected
 from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH ,
 CH_2OCOCH_3 , CH_2Cl , Cl, CH_2OCH_3 , $CH_2OCH(CH_3)_2$, I, CHO,
 CH_2CO_2H , $CH(CH_3)CO_2H$, , $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,
 $-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2$ -, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$,
 15 $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2 -adamantyl,
 $-CH_2NHCO_2$ -(1-naphthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$,
 $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$,
 $-CH_2NHCONH$ -(1-naphthyl), $-CH_2NHCONH$ -(1-adamantyl), CO_2H ,
 $-CH_2CH_2CO-N$ -, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, -
 20 $CH_2CH_2CH_2F$, $-CH_2SH$ and $-CH_2O$ -;

wherein each of R^3 through 11 is hydrido, with the proviso
 that at least one of R^5 , R^6 , R^8 and R^9 is an acidic group
 selected from CO_2H , SH, PO_3H_2 , SO_3H , $CONHNH_2$, $CONHNHSO_2CF_3$,
 OH,

25

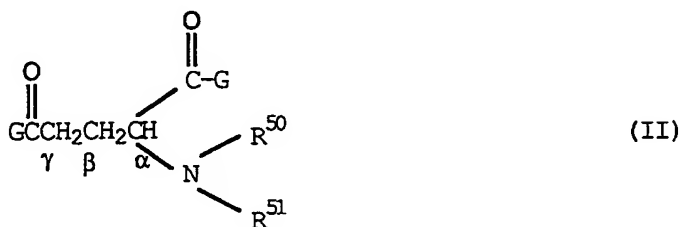


wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

The second component of a conjugate of the invention is provided by a residue which forms a kidney-enzyme-cleavable amide bond with the residue of the first-component AII antagonist compound. Such residue is preferably selected from a class of compounds of Formula II:



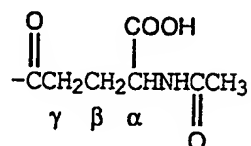
wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxycarbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-OR^{52}$, $-SR^{53}$ and $-NR^{54}$ wherein each of R^{52} , R^{53} and R^{54} is independently selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

More preferred are compounds of Formula II wherein each G is hydroxy.

- A more highly preferred class of compounds within Formula II consists of those compounds wherein each G is hydroxy; wherein R⁵⁰ is hydrido; and wherein R⁵¹ is selected from

- $$\begin{array}{c} \text{O} \\ || \\ -\text{CR}^{55} \end{array}$$
 wherein R⁵⁵ is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

- A most highly preferred compound of Formula II is N-acetyl- γ -glutamic acid which provides a residue for the second component of a conjugate of the invention as shown below:



- The phrase "terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino terminal moiety" characterizes a structural requirement for selection of a suitable angiotensin II antagonist compound as the "active" first residue of a conjugate of the invention. Such terminal amino moiety must be available to react with a terminal carboxylic moiety of the cleavable second residue to form a kidney-enzyme-specific hydrolyzable bond.

- In one embodiment of the invention, the first component used to form a conjugate of the invention provides a first residue derived from an AII antagonist compound

containing a terminal primary or secondary amino moiety. Examples of such terminal amino moiety are amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups such as aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

In another embodiment of the invention, the first component used to form the conjugate of the invention provides a first residue derived from an AII antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety. An example of a moiety convertible to an amino terminal moiety is a carboxylic acid group reacted with hydrazine so as to convert the acid moiety to carboxylic acid hydrazide. The hydrazide moiety thus contains the terminal amino moiety which may then be further reacted with the carboxylic acid containing residue of the second component to form a hydrolyzable amide bond. Such hydrazide moiety thus constitutes a "linker" group between the first and second components of a conjugate of the invention.

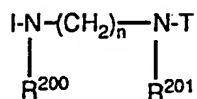
Suitable linker groups may be provided by a class of diamino-terminated linker groups based on hydrazine as defined by Formula III:



wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is

zero or a number selected from three through seven, inclusive. In Table I there is shown a class of specific examples of diamino-terminated linker groups within Formula III, identified as Linker Nos. 1-73. These linker groups would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of a carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

10

TABLE I

I = inhibitor
T = acetyl- γ -glutamyl

LINKER NO.	n	R ²⁰⁰	R ²⁰¹
1	0	H	H
2	0	CH ₃	H
3	0	C ₂ H ₅	H
4	0	C ₃ H ₇	H
5	0	CH(CH ₃) ₂	H
6	0	C ₄ H ₉	H
7	0	CH(CH ₃)CH ₂ CH ₃	H
8	0	C(CH ₃) ₃	H
9	0	C ₅ H ₉	H
10	0	C ₆ H ₁₁ (cyclo)	H
11	0	C ₆ H ₅	H

LINKER NO.	n	R ²⁰⁰	R ²⁰¹
12	0	CH ₂ C ₆ H ₅	H
13	0	H	CH ₃
14	0	H	C ₂ H ₅
15	0	H	C ₃ H ₇
16	0	H	CH(CH ₃) ₂
17	0	H	C ₄ H ₉
18	0	H	CH(CH ₃)CH ₂ CH ₃
19	0	H	C(CH ₃) ₃
20	0	H	C ₅ H ₉
21	0	H	C ₆ H ₁₃
22	0	H	C ₆ H ₅
23	0	H	CH ₂ C ₆ H ₅
24	0	H	C ₆ H ₁₁ (cyclo)
25	0	C ₆ H ₁₃	H
26	0	CH ₃	CH ₃
27	0	C ₂ H ₅	C ₂ H ₅

SUBSTITUTE SHEET

LINKER NO.	n	R ²⁰⁰	R ²⁰¹
28	0	C ₃ H ₇	C ₃ H ₇
29	0	CH(CH ₃) ₂	CH(CH ₃) ₂
30	0	C ₄ H ₉	C ₄ H ₉
31	0	CH(CH ₃)CH ₂ CH ₃	CH(CH ₃)CH ₂ CH ₃
32	0	C(CH ₃) ₃	C(CH ₃) ₃
33	0	C ₅ H ₉	C ₅ H ₉
34	0	C ₆ H ₁₃	C ₆ H ₁₃
35	0	C ₆ H ₁₁ (cyclo)	C ₆ H ₁₁ (cyclo)
36	0	C ₆ H ₅	C ₆ H ₅
37	0	CH ₂ C ₆ H ₅	CH ₂ C ₆ H ₅
38	3	H	H
39	3	CH ₃	H
40	3	H	CH ₃
41	3	C ₆ H ₅	H
42	3	H	C ₆ H ₅

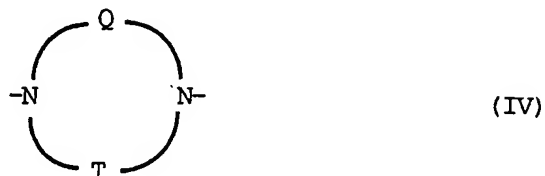
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LINKER NO.	n	R ²⁰⁰	R ²⁰¹
43	3	CH ₃	C ₆ H ₅
44	3	C ₆ H ₅	CH ₃
45	3	CH ₂ C ₆ H ₅	H
46	3	H	CH ₂ C ₆ H ₅
47	4	H	H
48	4	CH ₃	H
49	4	H	CH ₃
50	4	C ₆ H ₅	H
51	4	H	C ₆ H ₅
52	4	CH ₃	C ₆ H ₅
53	4	C ₆ H ₅	CH ₃
54	4	CH ₂ C ₆ H ₅	H
55	4	H	CH ₂ C ₆ H ₅
56	5	H	H
57	5	CH ₃	H
58	5	H	CH ₃

SUBSTITUTE SHEET

LINKER NO.	n	R ²⁰⁰	R ²⁰¹
59	5	C ₆ H ₅	H
60	5	H	C ₆ H ₅
61	5	CH ₃	C ₆ H ₅
62	5	C ₆ H ₅	CH ₃
63	5	CH ₂ C ₆ H ₅	H
64	5	H	CH ₂ C ₆ H ₅
65	6	H	H
66	6	CH ₃	H
67	6	H	CH ₃
68	6	C ₆ H ₅	H
69	6	H	C ₆ H ₅
70	6	CH ₃	C ₆ H ₅
71	6	C ₆ H ₅	CH ₃
72	6	CH ₂ C ₆ H ₅	H
73	6	H	CH ₂ C ₆ H ₅

Another class of suitable diamino terminal linker groups is defined by Formula IV:



5

wherein each of Q and T is one or more groups independently selected from



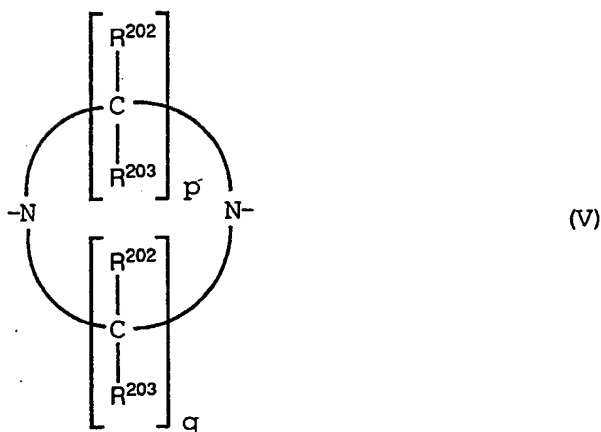
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wherein each of R²⁰² through R²⁰⁵ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

15

A preferred class of linker groups within Formula IV is defined by Formula V:

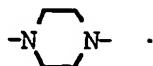
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wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

A more preferred class of linker groups of Formula V consists of divalent radicals wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive. Even more preferred are linker groups wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three. Most preferred is a linker group wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two; such most preferred linker

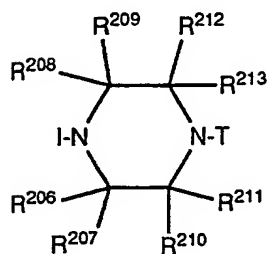
group is derived from a piperazinyl group and has the structure



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In Table II there is shown a class of specific examples of cyclized, diamino-terminated linker groups within Formula V. These linker groups, identified as Linker Nos. 74-
10 95, would be suitable to form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

15

TABLE II

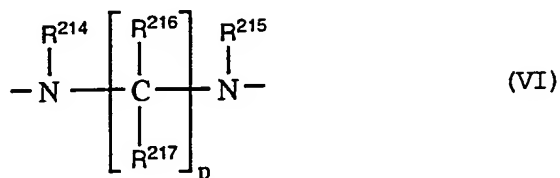
I = inhibitor
T = acetyl-γ-glutamyl

LINKER NO.	R206	R207	R208	R209	R210	R211	R212	R213
74	H	H	H	H	H	H	H	H
75	CH ₃	H	H	H	H	H	H	H
76	H	H	H	H	CH ₃	H	H	H
77	CH ₃	H	H	H	CH ₃	H	H	H
78	CH ₃	H	CH ₃	H	H	H	H	H
79	CH ₃	H	H	H	H	H	CH ₃	H
80	CH ₃	CH ₃	H	H	H	H	H	H
81	H	H	H	H	CH ₃	CH ₃	H	H
82	CH ₃	CH ₃	H	H	CH ₃	CH ₃	H	H
83	CH ₃	CH ₃	CH ₃	CH ₃	H	H	H	H

LINKER NO.	R206	R207	R208	R209	R210	R211	R212	R213
84	CH ₃	CH ₃	H	H	H	H	CH ₃	CH ₃
85	H	H	H	H	CH ₃	CH ₃	CH ₃	CH ₃
86	C ₆ H ₅	H	H	H	H	H	H	H
87	H	H	H	H	C ₆ H ₅	H	H	H
88	C ₆ H ₅	H	H	H	C ₆ H ₅	H	H	H
89	C ₆ H ₅	H	H	H	H	H	C ₆ H ₅	H
90	C ₆ H ₅	H	C ₆ H ₅	H	H	H	H	H
91	CH ₂ C ₆ H ₅	H	H	H	H	H	H	H
92	H	H	H	H	CH ₂ C ₆ H ₅	H	H	H
93	CH ₂ C ₆ H ₅	H	H	H	CH ₂ C ₆ H ₅	H	H	H
94	CH ₂ C ₆ H ₅	H	H	H	H	H	CH ₂ C ₆ H ₅	H
95	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	H	H	H	H	H

SUBSTITUTE SHEET

Another class of suitable diamino terminal linker groups is defined by Formula VI:

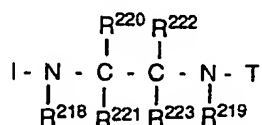


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wherein each of R²¹⁴ through R²¹⁷ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

A preferred class of linker groups within Formula VI consists of divalent radicals wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R²¹⁶ and R²¹⁷ is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three. A more preferred class of linker groups within Formula VI consists of divalent radicals wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R²¹⁶ and R²¹⁷ is independently selected from hydrido and alkyl; and wherein p is two. A specific example of a more preferred linker within Formula VI is the divalent radical ethylenediamino. In Table III there is shown a class of specific examples of diamino-terminated linker groups within Formula VI. These linker groups, identified as Linker Nos. 96-134, would be suitable to

form a conjugate between a carbonyl moiety of an AII antagonist (designated as "I") and a carbonyl moiety of carbonyl terminated second residue such as the carbonyl moiety attached to the gamma carbon of a glutamyl residue (designated as "T").

TABLE III

I = inhibitor
G = acetyl- γ -glutamyl

LINKER NO.	R ²¹⁸	R ²¹⁹	R ²²⁰	R ²²¹	R ²²²	R ²²³
96	H	H	H	H	H	H
97	H	H	H	H	H	CH ₃
98	H	H	H	CH ₃	H	H
99	H	H	H	CH ₃	H	CH ₃
100	CH ₃	H	H	H	H	H
101	H	CH ₃	H	H	H	H
102	H	H	H	H	CH ₃	CH ₃
103	H	H	CH ₃	CH ₃	H	H

LINKER NO.	R ²¹⁸	R ²¹⁹	R ²²⁰	R ²²¹	R ²²²	R ²²³
104	CH ₃	CH ₃	H	H	H	H
105	H	H	H	H	H	C ₆ H ₅
106	H	H	H	C ₆ H ₅	H	H
107	H	H	H	C ₆ H ₅	H	C ₆ H ₅
108	C ₆ H ₅	H	H	H	H	H
109	H	C ₆ H ₅	H	H	H	H
110	H	H	H	H	C ₆ H ₅	C ₆ H ₅
111	H	H	C ₆ H ₅	C ₆ H ₅	H	H
112	C ₆ H ₅	C ₆ H ₅	H	H	H	H
113	H	H	H	H	H	C ₂ H ₅
114	H	H	H	C ₂ H ₅	H	H
115	H	H	H	C ₂ H ₅	H	C ₂ H ₅
116	C ₂ H ₅	H	H	H	H	H
117	H	C ₂ H ₅	H	H	H	H
118	H	H	H	H	C ₂ H ₅	C ₂ H ₅

SUBSTITUTE SHEET

LINKER NO.	R ²¹⁸	R ²¹⁹	R ²²⁰	R ²²¹	R ²²²	R ²²³
119	H	H	C ₂ H ₅	C ₂ H ₅	H	H
120	C ₂ H ₅	C ₂ H ₅	H	H	H	H
121	CH ₃	H	C ₆ H ₅	H	H	H
122	CH ₃	H	H	H	C ₆ H ₅	H
123	H	CH ₃	C ₆ H ₅	H	H	H
124	H	CH ₃	H	H	C ₆ H ₅	H
125	CH ₃	CH ₃	H	C ₆ H ₅	H	H
126	CH ₃	CH ₃	H	H	H	C ₆ H ₅
127	H	H	H	H	H	CH ₂ C ₆ H ₅
128	H	H	H	CH ₂ C ₆ H ₅	H	H
129	CH ₂ C ₆ H ₅	H	H	H	H	H
130	H	CH ₂ C ₆ H ₅	H	H	H	H
131	CH ₃	H	CH ₂ C ₆ H ₅	H	H	H
132	CH ₃	H	H	H	CH ₂ C ₆ H ₅	H
133	H	CH ₃	CH ₂ C ₆ H ₅	H	H	H

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LINKER NO.	R ²¹⁸	R ²¹⁹	R ²²⁰	R ²²¹	R ²²²	R ²²³
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134	H	CH ₃	H	H	CH ₂ C ₆ H ₅	H
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The term "hydrido" denotes a single hydrogen atom (H) which may be attached, for example, to a carbon atom to form a hydrocarbyl group or attached to an oxygen atom to form an hydroxyl group. Where the term "alkyl" is used, either alone or within other terms such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having one to about twenty carbon atoms or, preferably, one to about twelve carbon atoms. More preferred alkyl radicals are "lower alkyl" radicals having one to about ten carbon atoms. Most preferred are lower alkyl radicals having one to about five carbon atoms. The term "cycloalkyl" embraces cyclic radicals having three to about ten ring carbon atoms, preferably three to about six carbon atoms, such as cyclopropyl and cyclobutyl. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo groups, preferably selected from bromo, chloro and fluoro. Specifically embraced by the term "haloalkyl" are monohaloalkyl, dihaloalkyl and polyhaloalkyl groups. A monohaloalkyl group, for example, may have either a bromo, a chloro, or a fluoro atom within the group. Dihalalkyl and polyhaloalkyl groups may be substituted with two or more of the same halo groups, or may have a combination of different halo groups. A dihaloalkyl group, for example, may have two fluoro atoms, such as difluoromethyl and difluorobutyl groups, or two chloro atoms, such as a dichloromethyl group, or one fluoro atom and one chloro atom, such as a fluoro-chloromethyl group. Examples of a polyhaloalkyl are trifluoromethyl, 1,1-difluoroethyl, 2,2,2-trifluoroethyl, perfluoroethyl and 2,2,3,3-tetrafluoropropyl

groups. The term "difluoroalkyl" embraces alkyl groups having two fluoro atoms substituted on any one or two of the alkyl group carbon atoms. Preferably, when the difluoroalkyl group is attached at the triazole ring R¹ and R² positions of

5 Formula I, the two fluoro atoms are substituted on the carbon atom which is attached directly to the triazole ring. Such preferred difluoroalkyl group may be characterized as an "alpha-carbon difluoro-substituted difluoroalkyl group" The terms "alkylol" and "hydroxyalkyl" embrace linear or branched

10 alkyl groups having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl groups. The term "alkenyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably three to about ten carbon atoms, and containing at least one carbon-carbon

15 double bond, which carbon-carbon double bond may have either cis or trans geometry within the alkenyl moiety. The term "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon triple bond.

20 The term "cycloalkenyl" embraces cyclic radicals having three to about ten ring carbon atoms including one or more double bonds involving adjacent ring carbons. The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon

25 atoms, such as methoxy group. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy groups attached to the alkyl radical, that is, to form monoalkoxyalkyl and dialkoxyalkyl groups. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or

30 more halo atoms, such as fluoro, chloro or bromo, to provide haloalkoxy or haloalkoxyalkyl groups. The term "alkylthio" embraces radicals containing a linear or branched alkyl group, of one to about ten carbon atoms attached to a divalent sulfur atom, such as a methythio group. The term "aryl" embraces

35 aromatic radicals such as phenyl, naphthyl and biphenyl. The

term "aralkyl" embraces aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, phenylbutyl and diphenylethyl. The terms "benzyl" and "phenylmethyl" are interchangeable. The terms "aryloxy" and "arylthio" denote radical respectively, aryl groups having an oxygen or sulfur atom through which the radical is attached to a nucleus, examples of which are phenoxy and phenylthio. The terms "sulfinyl" and "sulfonyl", whether used alone or linked to other terms, denotes respectively divalent radicals SO and SO₂. The term "aralkoxy", alone or within another term, embraces an aryl group attached to an alkoxy group to form, for example, benzyloxy. The term "acyl" whether used alone, or within a term such as acyloxy, denotes a radical provided by the residue after removal of hydroxyl from an organic acid, examples of such radical being acetyl and benzoyl. The term "heteroaryl" embraces aromatic ring systems containing one or two hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five or six ring members, examples of which are thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl. Such heteroaryl may be attached as a substituent through a carbon atom of the heteroaryl ring system, or may be attached through a carbon atom of a moiety substituted on a heteroaryl ring-member carbon atom, for example, through the methylene substituent of imidazolemethyl moiety. Also, such heteroaryl may be attached through a ring nitrogen atom as long as aromaticity of the heteroaryl moiety is preserved after attachment.

Specific examples of alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, methylbutyl, dimethylbutyl and neopentyl. Typical alkenyl and alkynyl groups may have one unsaturated bond, such as an allyl group, or may have a plurality or unsaturated bonds, with such plurality of bonds

either adjacent, such as allene-type structures, or in conjugation, or separated by several saturated carbons.

Conjugates of the invention formed from compounds of Formula I have been found to inhibit the action of angiotensin II in mammals. For example, specific biphenylmethyl 1H-substituted-imidazole compounds within Formula I have been evaluated for angiotensin II receptor binding and antihypertensive effects in renal hypertensive rats, as shown in EP #253,310 published 20 January 1988. Thus, conjugates of Formula I are therapeutically useful in methods for treating hypertension by administering to a hypertensive patient a therapeutically-effective amount of a conjugate containing a compound of Formula I, such that the conjugate is hydrolyzed by an enzyme found predominantly in the kidney so as to release an active angiotensin II antagonist species. The phrase "hypertensive patient" means, in this context, a mammalian subject suffering from the effects of hypertension or susceptible to a hypertensive condition if not treated to prevent or control such hypertension.

Included within the invention are conjugates of compounds of Formula I which are tautomeric forms of the described compounds, isomeric forms including diastereoisomers, and the pharmaceutically-acceptable salts thereof. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric and

phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, example of which are formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, p-hydroxybenzoic, salicylic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, 2-hydroxyethanesulfonic, pantothenic, benzenesulfonic, toluenesulfonic, sulfanilic, mesylic, cyclohexylaminosulfonic, stearic, algenic, β -hydroxy butyric, malonic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formula I include metallic salts made from aluminium, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. All of these salts may be prepared by conventional means from the corresponding compound of Formula I by reacting, for example, the appropriate acid or base with the compound of Formula I. Also, such pharmaceutical salts may be formed with either a compound of Formula I which is contained in the conjugate, or such salts may be formed with the conjugate itself.

Conjugates of the invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or non-racemic mixtures thereof. The optical isomers can be obtained by resolution of the racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyltartaric, dibenzoyltartaric, ditoluoyltartaric and camphorsulfonic acid and then separation of the mixture of

diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting conjugates with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active conjugates can likewise be obtained by utilizing optically active starting materials. These isomers may be in the form of a free acid, a free base, an ester or a salt.

Conjugates of the invention may be prepared using precursors of highly active angiotensin II antagonists of Formula I. Examples of lesser active, suitable precursors are acid chloride, esters and amides of angiotensin II antagonists of Formula I. For example, ester precursors of angiotensin II antagonists, such as the methyl ester precursor made in Step 1 of Example 81, may be reacted with hydrazine to provide an amino terminal moiety which then can be reacted with a glutamic acid derivative to form a conjugate of the invention. Such precursors or intermediates themselves may be relatively strong, relatively weak, or inactive as AII antagonists. Also, conjugates of the invention may be prepared using angiotensin II antagonists lacking a reactive terminal amino moiety. Such angiotensin II antagonists, as shown in Example Nos. 78-80 of Table IV, lack a terminal amino moiety. These AII antagonist compounds may be modified as described in

Example Nos. 711 and 712 to contain a terminal acid moiety which then may be connected to a glutamyl residue through a diamino-terminated linker group, such as shown in Tables I-III.

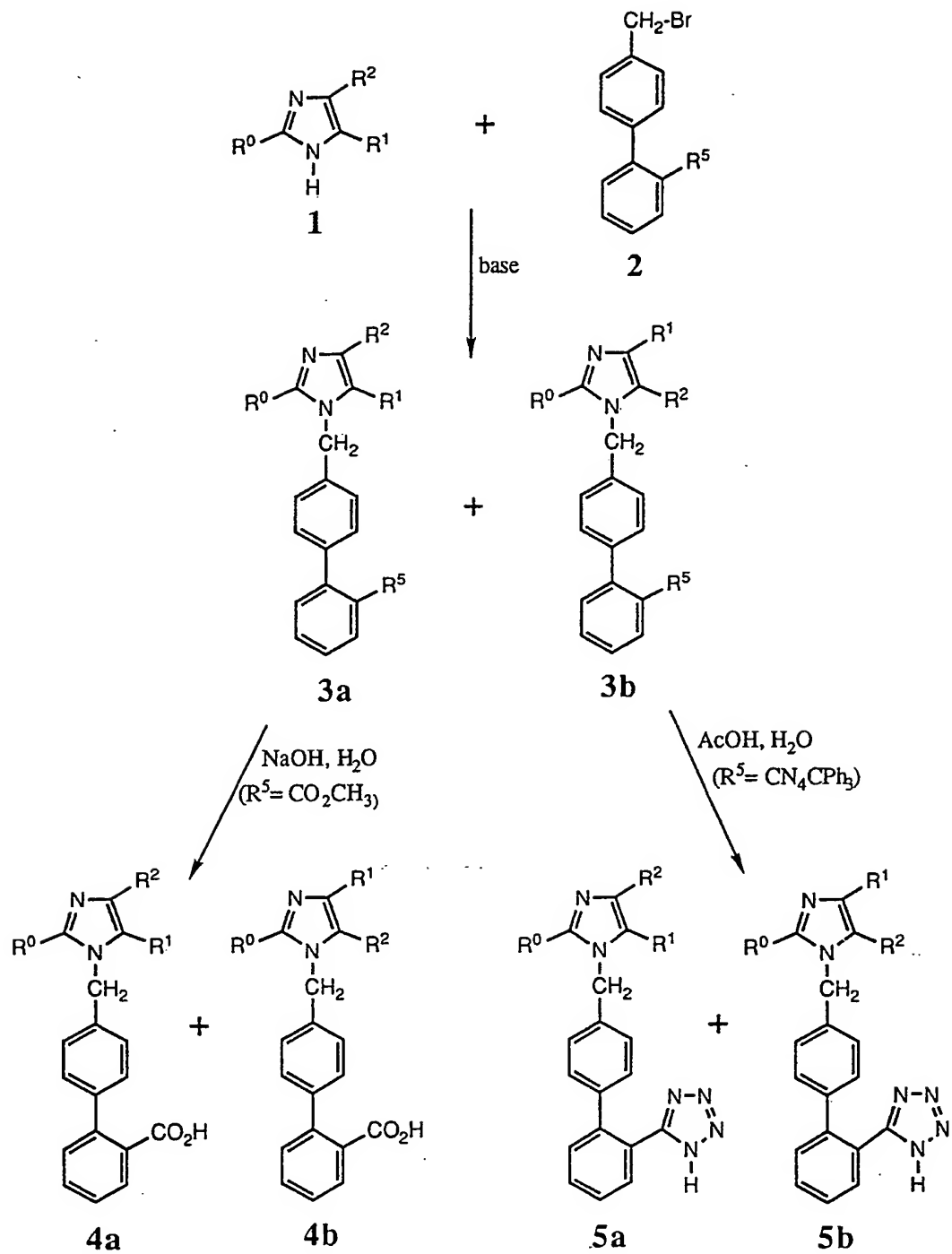
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Synthetic Procedures

Conjugates of the invention are synthesized by
10 reaction between precursors of the first and second residues. One of such precursors must contain a reactive acid moiety, and the other precursor must contain a reactive amino moiety, so that a conjugate is formed having a cleavable bond. Either precursor of the first and second
15 residues may contain such reactive acid or amino moieties. Preferably, the precursors of the first residue are angiotensin II antagonists and will contain a reactive amino moiety or a moiety convertible to a reactive amino moiety. Inhibitor compounds lacking a reactive amino
20 moiety may be chemically modified to provide such reactive amino moiety. Chemical modification of these inhibitor compounds lacking a reactive amino group may be accomplished by reacting an acid or an ester group on an AII antagonist compound with an amino compound having at
25 least one reactive amino moiety. A suitable amino compound would be a diamino compound such as hydrazine, urea or ethylenediamine. Hydrazine, for example, may be reacted with a carboxylic acid or ester moiety of an AII antagonist compound to form a hydrazide derivative of such AII
30 antagonist compound.

In the following general Synthetic Procedures, there is described firstly in Scheme I, methods for making suitable angiotensin II antagonists of Formula I for selection as the first component of the conjugate. Then, in Schemes II-
5 VII, there are described general methods for making a conjugate by reacting a first component AII antagonist of Formula I with a cleavable second component represented by N-acetyl- γ -glutamic acid.

Scheme I

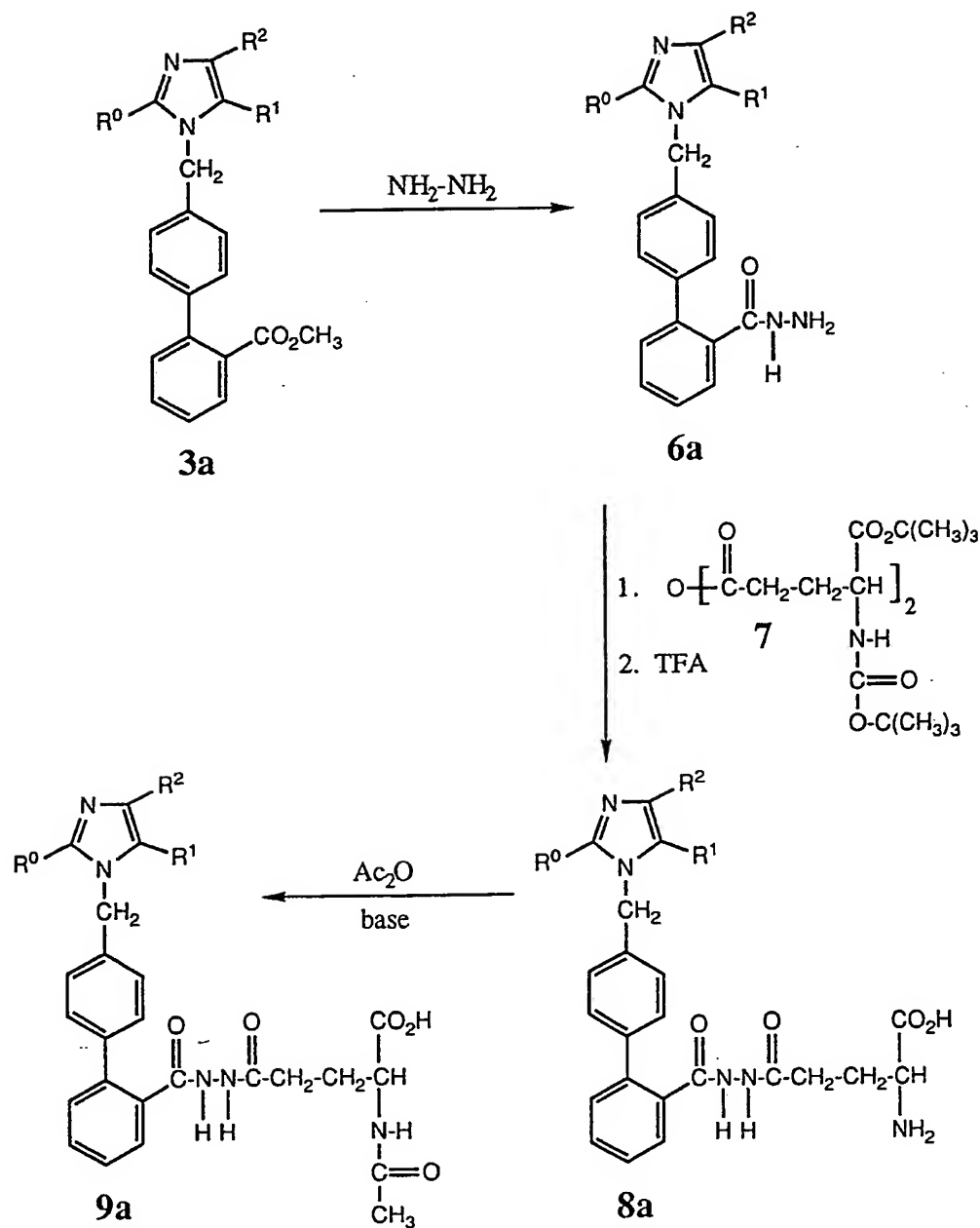


Synthetic Scheme I shows the coupling reaction of trisubstituted imidazoles 1 with the appropriate alkylating reagent 2. In the first step, 1 and 2 are reacted in

5 dimethylformamide (DMF) in the presence of base, such as cesium carbonate, and a dehydrating agent, such as molecular sieves, to give a mixture of coupled regioisomers 3a and 3b. The isomer mixture may be converted to mixtures of the corresponding acids 4a and 4b or tetrazoles 5a and 5b. Or,

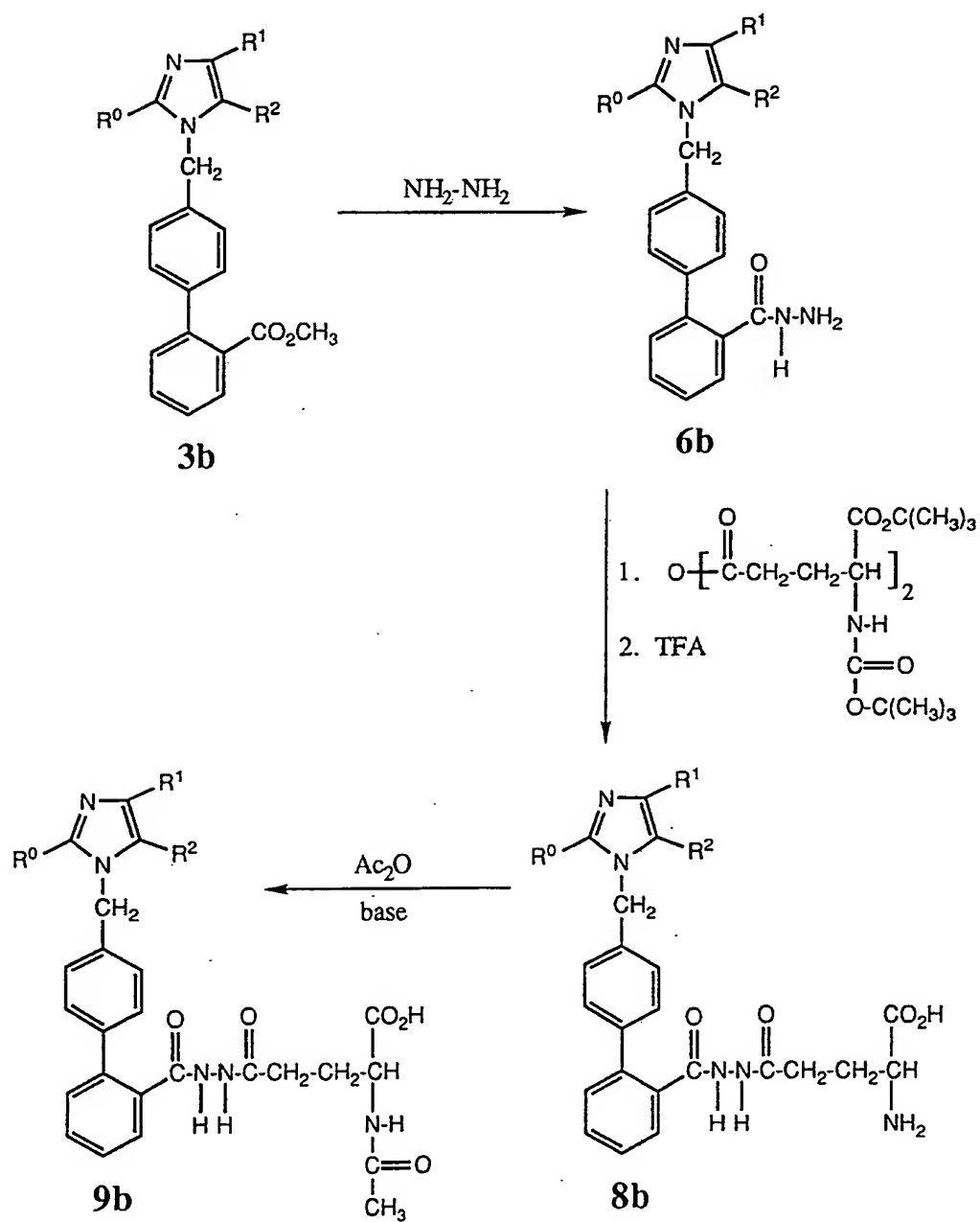
10 the isomers 3a and 3b may be separated by chromatographic methods, and each isomer may be reacted with the appropriate reagent to provide the acid- or tetrazole-substituted end product.

Scheme II



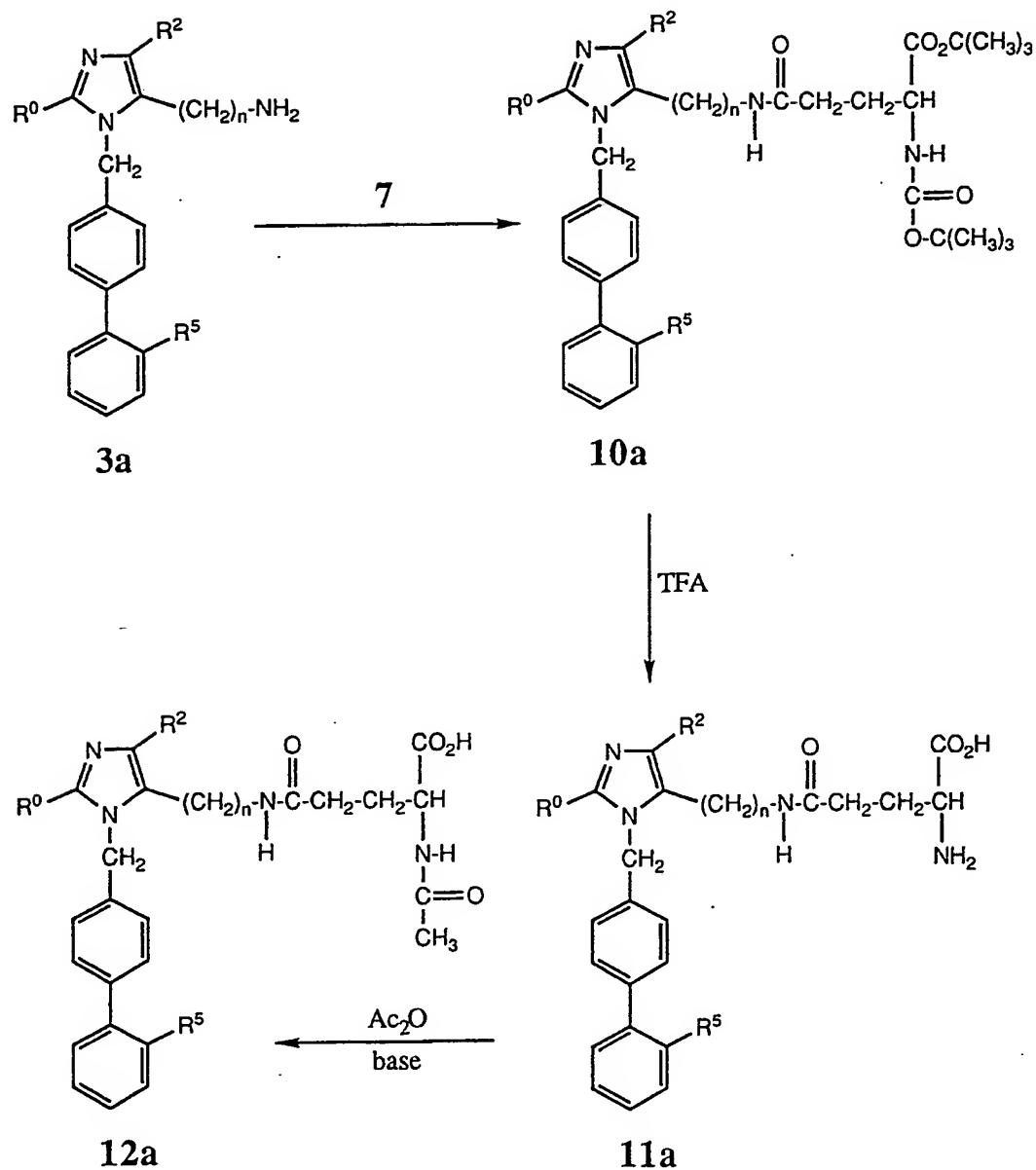
Synthetic Scheme II shows the preparation of the renal-selective angiotensin II antagonists by coupling γ -glutamic acid with one of the angiotensin II antagonist regiosomers 3a (the synthesis of the other regioisomer is shown in Scheme III); the biphenyl R⁵ acid moiety of the AII antagonist is coupled to the γ -acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3a is converted to the hydrazide 6a by the action of hydrazine. In step 2, the hydrazide 6a is first reacted with the symmetrical anhydride of the protected γ -glutamic acid 7 and subsequently reacted with trifluoroacetic acid (TFA) to give the deprotected coupled material 8a. In Step 3, the free amino group of 8a is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 9a.

Scheme III



Synthetic Scheme III shows the preparation of renal-selective angiotensin II antagonists by coupling γ -glutamic acid with one of the angiotensin II antagonist regioisomers 3b (the synthesis of the other regioisomer is shown in Scheme II); the biphenyl R⁵ acid moiety of the AII antagonist is coupled to the γ -acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3b is converted to the hydrazide 6b by the action of hydrazine. In step 2, the hydrazide 6b is first reacted with the symmetrical anhydride of the protected γ -glutamic acid 7 and subsequently reacted with TFA to give the deprotected coupled material 8b. In step 3, the free amino group of 8b is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 9b.

Scheme IV

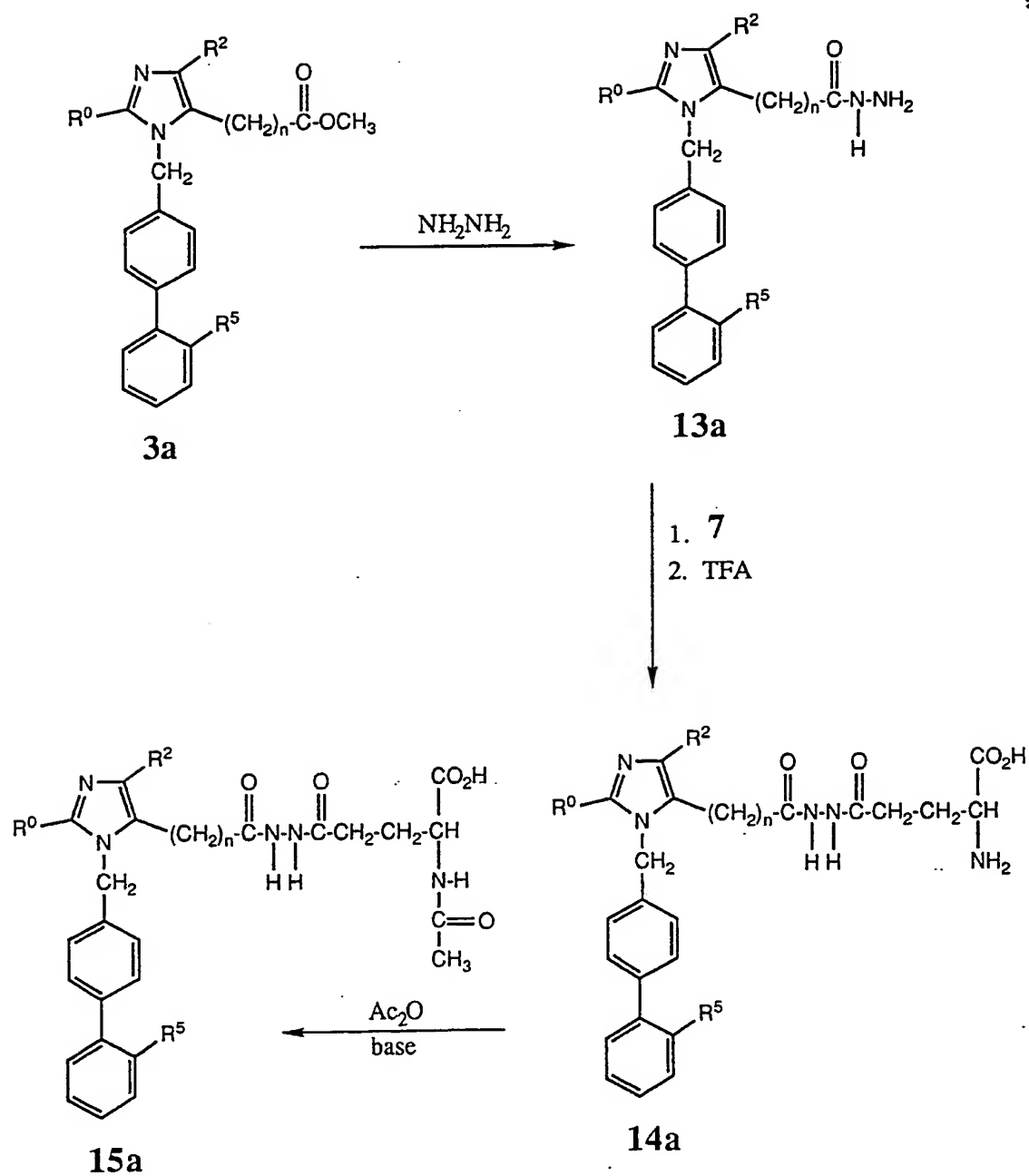


Synthetic Scheme IV shows the preparation of renal-selective angiotensin II antagonists by coupling γ -glutamic acid with one of the angiotensin II antagonist regioisomers 3a which contains an amino moiety in the imidazole R¹ group (the synthesis of the other regioisomer is shown in Scheme V). In step 1, the AII antagonist 3a is reacted with the symmetrical anhydride of the protected γ -glutamic acid 7 to give 10a. In step 2, the protected material 10a is reacted with TFA to give the deprotected coupled material 11a. In step 3, the free amino compound 11a is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 12a.



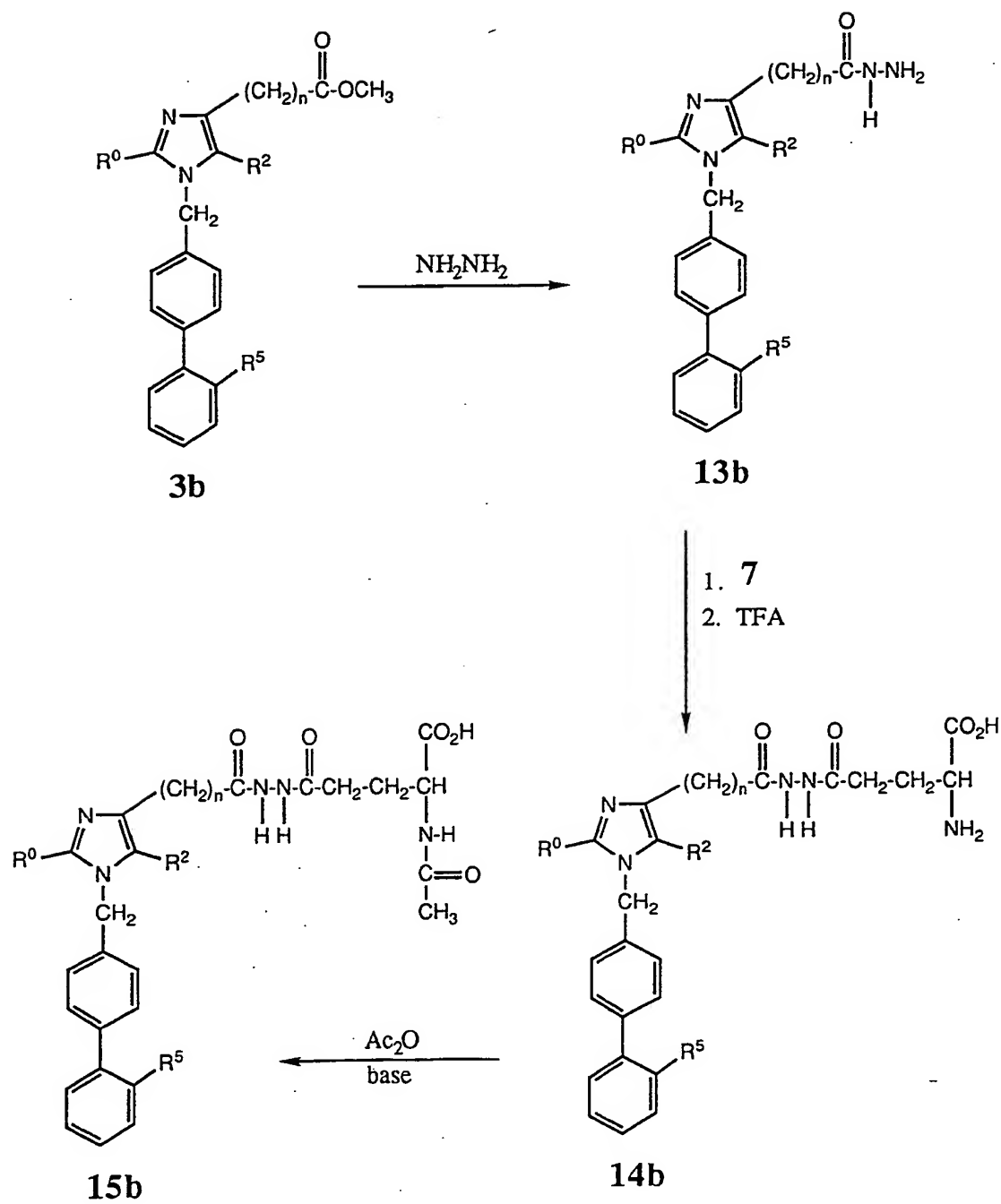
Synthetic Scheme V shows the preparation of renal-selective angiotensin II antagonists by coupling γ -glutamic acid with one of the angiotensin II antagonist regioisomers 3b which contains an amino moiety in the imidazole R¹ group (the synthesis of the other regioisomer is shown in Scheme IV). In step 1, the AII antagonist 3b is reacted with the symmetrical anhydride of the protected γ -glutamic acid 7 to give 10b. In step 2, the protected material 10b is reacted with TFA to give the deprotected coupled material 11b. In step 3, the free amino compound 11b is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 12b.

Scheme VI



Synthetic Scheme VI shows the preparation of renal-selective angiotensin II antagonists by coupling γ -glutamic acid with one of the angiotensin II antagonist regioisomers 3a which contains an acid moiety in the imidazole R¹ group (the synthesis of the other regioisomer is shown in Scheme VII); the imidazole R¹ acid moiety of the AII antagonist is coupled to the γ -acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3a is converted to the hydrazide 13a by the action of hydrazine. In step 2, the hydrazide 13a is first reacted with the symmetrical anhydride of the protected γ -glutamic acid 7 and subsequently reacted with TFA to give the deprotected coupled material 14a. In step 3, the free amino group of 14a is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 15a.

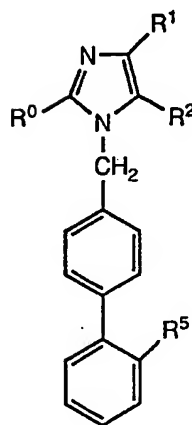
Scheme VII



Synthetic Scheme VII shows the preparation of renal-selective angiotensin II antagonists by coupling γ -glutamic acid with one of the angiotensin II antagonist regioisomers 3b which contains an acid moiety in the imidazole R¹ group (the synthesis of the other isomer is shown in Scheme VII); the imidazole R¹ acid moiety of the AII antagonist is coupled to the γ -acid moiety of glutamic acid via an hydrazine linker. In step 1, the methyl ester of the AII antagonist 3b is converted to the hydrazide 13b by the action of hydrazine. In step 2, the hydrazide 13b is first reacted with the symmetrical anhydride of the protected γ -glutamic acid 7 and subsequently reacted with TFA to give the deprotected coupled material 14b. In step 3, the free amino group of 14b is acetylated with acetic anhydride in the presence of base to give the renal-selective angiotensin II antagonist 15b.



The following Examples 1-80 shown in Table IV are angiotensin II antagonists suitable for selection as precursors to provide the first residue of a conjugate of the invention. These angiotensin II antagonists may be prepared generally by the procedures outlined above in Scheme I. Also, specific procedures for preparation of Examples 1-80 of Table IV may be found in EP #253,310 published 20 January 1988.

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TABLE IV

Ex. #	R^0	R^2	R^1	R^5
1	C ₄ H ₉ (n)	CH ₂ OCOCH ₃	Cl	CO ₂ H
2	C ₄ H ₉ (n)	CH ₂ OH	NO ₂	CO ₂ H
3	C ₄ H ₉ (n)	CH ₂ OH	CF ₃	CO ₂ H
4	SC ₃ H ₇	CH ₂ OH	H	CO ₂ H
5	C ₄ H ₉ (n)	CH ₂ OH	Cl	CO ₂ H
6	C ₄ H ₉ (n)	Cl	CH ₂ OH	CO ₂ H

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Ex. #	R ⁰	R ²	R ¹	R ⁵
7	C ₄ H ₉ (n)	H	CH ₂ OH	CO ₂ H
8	C ₄ H ₉ (n)	CH ₂ OH	H	CO ₂ H
9	C ₄ H ₉ (n)	CH ₂ OCH ₃	Cl	CO ₂ H
10	C ₄ H ₉ (n)	CH ₂ OCH(CH ₃) ₂	Cl	CO ₂ H
11	C ₄ H ₉ (n)	CH ₂ OH	Br	CO ₂ H
12	C ₄ H ₉ (n)	CH ₂ OH	F	CO ₂ H
13	C ₄ H ₉ (n)	CH ₂ OH	I	CO ₂ H
14		CH ₂ OH	Cl	CO ₂ H
15		CH ₂ OH	Cl	CO ₂ H
16	C ₄ H ₉ (n)	I	CH ₂ OH	CO ₂ H
17	C ₃ H ₇ (n)	CH ₂ OH	Cl	CO ₂ H





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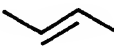
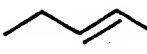
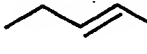

Ex. #	R ⁰	R ²	R ¹	R ⁵
18	C ₂ H ₅	CH ₂ OH	Cl	CO ₂ H
19	C ₃ H ₇ (n)	CH ₂ OH	Cl	CO ₂ H
20	C ₅ H ₁₁ (n)	CH ₂ OH	Cl	CO ₂ H
21	C ₆ H ₁₃ (n)	CH ₂ OH	Cl	CO ₂ H
22	C ₄ H ₉ (n)	CH ₂ SH	Cl	CO ₂ H
23	C ₄ H ₉ (n)	CH ₂ OC ₆ H ₅	Cl	CO ₂ H
24	C ₃ H ₇ (n)	CHO	Cl	CO ₂ H
25	C ₄ H ₉ (n)	CH ₂ CO ₂ H	Cl	CO ₂ H
26	C ₄ H ₉ (n)	CH(CH ₃)CO ₂ H	Cl	CO ₂ H
27	C ₄ H ₉ (n)	NO ₂	CH ₂ OH	CO ₂ H
28	C ₄ H ₉ (n)	CH ₂ OCOCH ₃	Cl	CO ₂ H

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Ex. #	R ⁰	R ²	R ¹	R ⁵
29	C ₄ H ₉ (n)	CH ₂ OCOCH ₂ CH ₂ - 	Cl	CO ₂ H
30	SC ₄ H ₉ (n)	CH ₂ OH	H	CO ₂ H
31	 -CH ₂ S	CH ₂ OH	H	CO ₂ H
32	C ₄ H ₉ (n)	CHO	Cl	CO ₂ H
33	C ₄ H ₉ (n)	CO ₂ CH ₃	Cl	CO ₂ H
34	C ₄ H ₉ (n)	CONH ₂	Cl	CO ₂ H
35		CH ₂ OH	Cl	CO ₂ H
36		CHO	Cl	CO ₂ H
37	C ₄ H ₉ (n)	CHO	H	CO ₂ H
38	C ₄ H ₉ (n)	CHO	CF ₃	CO ₂ H
39	C ₄ H ₉ (n)	CONHCH ₃	Cl	CO ₂ H

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
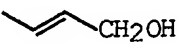
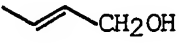

Ex. #	R ⁰	R ²	R ¹	R ⁵
40	C ₄ H ₉ (n)	CON(CH ₃) ₂	Cl	CO ₂ H
41		CH ₂ OH	Cl	CO ₂ H
42		CH ₂ OH	CF ₃	CO ₂ H
43		CHO	Cl	CO ₂ H
44	C ₄ H ₉ (n)	$\begin{array}{c} \text{O} \\ \parallel \\ \text{CH}_2\text{-N-C-OC}_2\text{H}_5 \\ \\ \text{H} \end{array}$	Cl	CO ₂ H
45	C ₄ H ₉ (n)	CH ₂ NHCO ₂ 	Cl	CO ₂ H
46	C ₄ H ₉ (n)	CH ₂ NHCO ₂ CH ₃	Cl	CO ₂ H
47	C ₄ H ₉ (n)	CH ₂ NHCO ₂ C ₃ H ₇	Cl	CO ₂ H
48	C ₄ H ₉ (n)	CH ₂ NHCO ₂ CH ₂ (CH ₃) ₂	Cl	CO ₂ H

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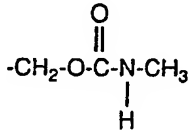
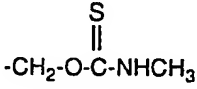
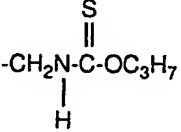
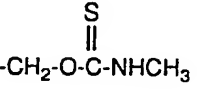
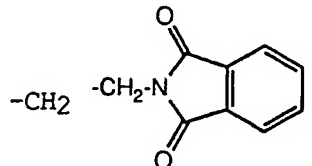
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Ex. #	R ⁰	R ²	R ¹	R ⁵
49	C ₄ H ₉ (n)	CH ₂ NHCO ₂ C ₄ H ₉	Cl	CO ₂ H
50	C ₄ H ₉ (n)	CH ₂ -NHCO ₂ -adamantyl	Cl	CO ₂ H
51	C ₃ H ₇ (n)	CH ₂ NHCO ₂ CH ₃	Cl	CO ₂ H
52	C ₄ H ₉ (n)	CH ₂ NHCO ₂ CH ₃	Cl	CO ₂ H
53	C ₄ H ₉ (n)	CH ₂ NHCO ₂ C ₂ H ₅	Cl	CO ₂ H
54	C ₄ H ₉ (n)	CH ₂ NHCO ₂ C ₃ H ₇	Cl	CO ₂ H
55	C ₄ H ₉ (n)	CH ₂ NHCO ₂ C ₄ H ₉	Cl	CO ₂ H
56	C ₄ H ₉ (n)	CH ₂ NHCO ₂ CH(CH ₃) ₂	Cl	CO ₂ H
57	C ₄ H ₉ (n)	CH ₂ NHCO ₂ (1-naphthyl)	Cl	CO ₂ H
58	C ₄ H ₉ (n)	CH ₂ NHCONHCH ₃	Cl	CO ₂ H
59	C ₄ H ₉ (n)	CH ₂ NHCONHC ₂ H ₅	Cl	CO ₂ H

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Ex. #	R ⁰	R ²	R ¹	R ⁵
60	C ₄ H ₉ (n)	CH ₂ NHCONHC ₃ H ₇	Cl	CO ₂ H
61	C ₄ H ₉ (n)	CH ₂ NHCONHC ₄ H ₉	Cl	CO ₂ H
62	C ₄ H ₉ (n)	CH ₂ NHCONHCH(CH ₃) ₂	Cl	CO ₂ H
63	C ₄ H ₉ (n)	CH ₂ NHCONH(1-naphthyl)	Cl	CO ₂ H
64	C ₃ H ₇ (n)	CH ₂ CH ₂ —C(=O)—N ₁ 	H	CO ₂ H
65	C ₃ H ₇ (n)	 CH ₂ OH	Cl	CO ₂ H
66	C ₃ H ₇ (n)	 CH ₂ OH	Cl	CO ₂ H
67	C ₄ H ₉ (n)	CH ₂ CH ₂ —C(=O)—N ₁ 	Cl	CO ₂ H
68	C ₄ H ₉ (n)	CH ₂ CH ₂ CO ₂ H	Cl	CO ₂ H
69	C ₄ H ₉ (n)	CH ₂ CH ₂ CH ₂ CH ₂ CO ₂ H	Cl	CO ₂ H

83

Ex. #	R ⁰	R ²	R ¹	R ⁵
70		CH ₂ OH	Cl	CO ₂ H
71	C ₄ H ₉ (n)		Cl	CO ₂ H
72	C ₄ H ₉ (n)		Cl	CO ₂ H
73	C ₄ H ₉ (n)		H	CO ₂ H
74	C ₄ H ₉ (n)		H	CO ₂ H
75	C ₄ H ₉ (n)	-CH ₂ CH ₂ CH ₂ F	Cl	CO ₂ H
76	C ₄ H ₉ (n)	-CH ₂ ONO ₂	Cl	CO ₂ H
77	C ₄ H ₉ (n)		Cl	CO ₂ H

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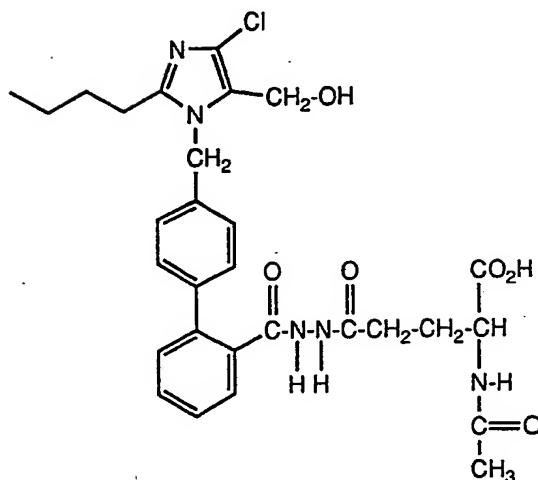
84

Ex. #	R ⁰	R ²	R ¹	R ⁵
78	C ₄ H ₉ (n)	CH ₂ OH	Cl	CN ₄ H
79	C ₄ H ₉ (n)	Cl	CH ₂ OH	CN ₄ H
80	C ₄ H ₉ (n)	CHO	Cl	CN ₄ H

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A class of highly preferred specific conjugates of the invention is provided by conjugates formed from a biphenylmethyl 1H-substituted imidazole AII antagonist compound linked to a cleavable glutamyl residue. Each conjugate contains a diamino linker moiety which connects a terminal carboxylic acid moiety on the biphenylmethyl portion of the AII antagonist compound with a terminal carboxylic acid moiety on the gamma carbon of the cleavable glutamyl residue. Such conjugates are shown herein as Examples 81-146. General procedures for preparation of the conjugates of Examples 81-146 are described in Schemes II-III. Detailed procedures for preparation of representative conjugates are described in Examples 81 and 82. Similar procedures may be used for preparation of the conjugates identified as Examples 83-146 shown in Table V.

Example 81



5 N-acetyl-L-glutamic acid, 5-[[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide

10 Step 1: Preparation of 1-[(2'-methoxycarbonyl-biphenyl-4-yl)methyl]-2-butyl-4-chloro-5-hydroxymethylimidazole.

Under nitrogen, a solution of 6.69 g (36 mmol) of 2-butyl-4-chloro-5-hydroxymethylimidazole in 100 mL of anhydrous dimethylformamide (DMF) was treated with molecular sieves and 11.0 g (36 mmol) of 4-bromomethyl-2'-methoxycarbonylbiphenyl. The reaction was allowed to stir at ambient temperature overnight and then was filtered. The DMF was removed *in vacuo* and the residue was partitioned between water and chloroform; the chloroform extracts were combined, dried (MgSO₄), and concentrated *in vacuo* giving 17.4 g of

crude material. Purification by silica gel chromatography (Waters Prep-500A) using ethyl acetate/hexane (40:60) gave the 4-hydroxymethyl isomer as the regioisomer with the lower R_f value and 6.27 g (42%) of the 5-hydroxymethyl isomer: NMR (CDCl₃) δ 0.91 (t, $J=7$ Hz, 3H), 1.29-1.44 (m, 2H), 1.52 (t, $J=8$ Hz, 1H), 1.63-1.76 (m, 2H), 2.62 (t, $J=7$ Hz, 2H), 3.65 (s, 3H), 4.54 (d, $J=8$ Hz, 2H), 7.02-7.08 (m, 2H), 7.25-7.36 (m, 3H), 7.38-7.47 (m, 1H), 7.50-7.58 (m, 1H), 7.83-7.90 (m, 1H).

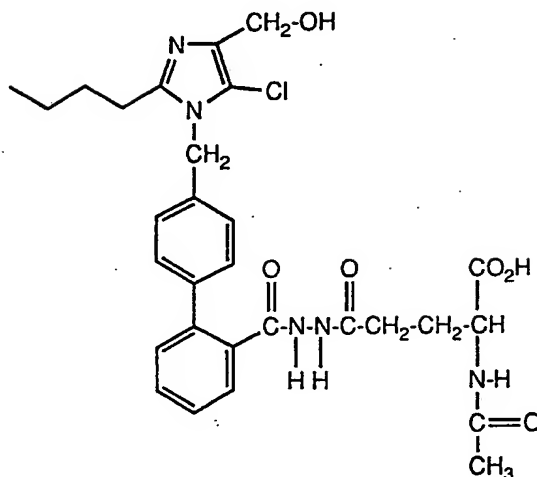
Step 2: Preparation of 1-[(2'-hydrazinylcarbonyl-biphenyl-4-yl)methyl]-2-butyl-4-chloro-5-hydroxymethylimidazole.

Under nitrogen, 6.27 g (15 mmol) of the 5-hydroxymethyl ester from step 1 was dissolved in 100 mL of methanol and treated with 15 mL (480 mmol) of anhydrous hydrazine. The reaction was allowed to stir at reflux overnight; concentration in vacuo gave 4.83 g of crude material. Purification by silica gel chromatography (Waters Prep-500A) using isopropanol/ethyl acetate (20:80) gave 4.27 g (68%) of the hydrazide as a colorless glass: NMR (CDCl₃) δ 0.81 (t, $J=7\text{Hz}$, 3H), 1.18-1.34 (m, 2H), 1.42-1.56 (m, 2H), 2.50 (t, $J=\text{Hz}$, 2H), 4.15-4.35 (br s, 2H), 4.35 (d, $J=8\text{Hz}$, 2H), 5.24 (t, $J=8\text{Hz}$, 1H), 7.05-7.13 (m, 2H), 7.32-7.44 (m, 5H), 7.45-7.54 (m, 1H), 9.34 (s, 1H).

Step 3: Preparation of N-acetyl-L-glutamic acid, 5-[[4'-(2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl)][1,1'-biphenyl]-2-yl]carbonylhydrazide.

5 To a solution of 1.70 g (5.60 mmol) of N-Boc-L-glutamic acid- α -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen was added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction was allowed to stir for 2 h and filtered under nitrogen. The anhydride
10 solution was then added to a solution of 1.0 g (2.4 mmol) of hydrazide from step 2 in 75 mL of methylene chloride under nitrogen. The reaction was stirred overnight, concentrated to a volume of 25 mL, cooled to 0°C, and treated with 25 mL of TFA under nitrogen. The stirred reaction was allowed to warm
15 to ambient temperature overnight and concentrated in vacuo. The crude product was dissolved in 100 mL of acetonitrile/water (1:1) and the pH adjusted to 8 with 1 M K₂CO₃. The solution was cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K₂CO₃ was
20 added every 30 min for 5 h; the pH was maintained at 9 and the reaction temperature kept below 5°C. After the last addition, the reaction was allowed to warm to ambient temperature overnight. The pH was adjusted to 4 with 3 M HCl and the reaction was concentrated to 100 mL. Purification by reverse
25 phase chromatography (Waters Deltaprep-3000) using isocratic 25% acetonitrile/water (0.05% TFA) gave 1.0 g (75% overall yield from the hydrazide of step 2) of colorless product: NMR (DMSO-d₆) δ 0.81 (t, J=7Hz, 3H), 1.20-1.30 (m, 2H), 1.42-1.55 (m, 2H), 1.75-1.84 (m, 2H), 1.85 (s, 3H), 1.89-2.05 (m, 2H),
30 2.21 (t, J=7Hz, 2H), 4.13-4.24 (m, 1H), 4.35 (s, 2H), 7.05-7.12 (m, 2H), 7.37-7.58 (m, 6H), 8.12-8.17 (m, 2H); MS (FAB) m/e (rel. intensity) 584 (18), 568 (100), 225 (64); HRMS. Calcd for M+H: 584.2276. Found: 584.2240.

Example 82



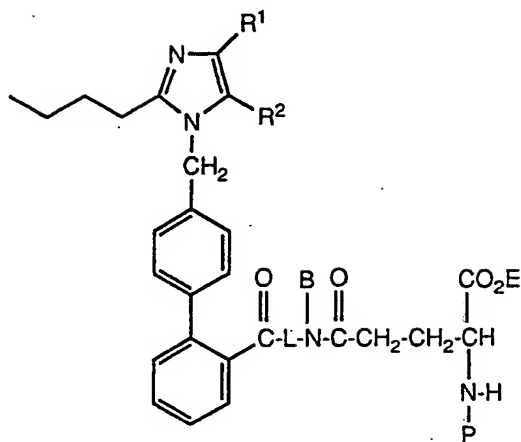
5 N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide

Step 1: Preparation of 1-[(2'-hydrazinylcarbonyl-biphenyl-4-yl)methyl]-2-butyl-5-chloro-4-hydroxymethylimidazole.

10 Under nitrogen, 4.13 g (10 mmol) of the 4-hydroxymethyl ester from step 1 of Example 81 is dissolved in 100 mL of methanol and is treated with 15 mL of (480 mmol) of anhydrous hydrazine. The reaction is allowed to stir at reflux overnight; concentration in vacuo gives the crude
15 material. Purification by silica gel chromatography (Waters Prep-500A) gives the pure hydrazide.

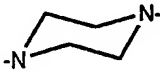
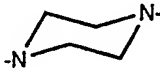
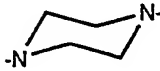
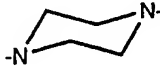
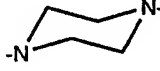
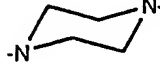
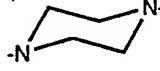
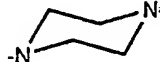
Step 2: Preparation of N-acetyl-L-glutamic acid, 5-[[4'-(2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl]][1,1'-biphenyl]-2-yl]carbonylhydrazide

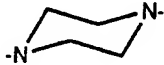
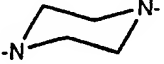
- 5 To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid- α -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride
- 10 solution is then added to a solution of 1.0 g (2.4 mmol) of the hydrazide from step 1 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed
- 15 to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K₂CO₃. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K₂CO₃ is
- 20 added every 30 min for 5 h; the pH is maintained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by
- 25 reverse phase chromatography (Waters Deltaprep-3000) gives the product.

TABLE V

Ex. #	R ²	R ¹	L	B	E	P
83	CH ₂ OH	Cl	-NH-	H	H	H
84	CH ₂ OH	Cl	-NH-	H	CH ₃	H
85	CH ₂ OH	Cl	-NH-	H	CH ₃	COCH ₃
86	CH ₂ OH	Cl	-NH-	H	C ₂ H ₅	COCH ₃
87	CH ₂ OH	Cl	-NH-	H	C ₂ H ₅	H
88	CH ₂ OH	Cl	-NH-	H	H	COCH ₂ Cl
89	CH ₂ OH	Cl	-NH-	H	H	COC ₄ H ₉ (n)

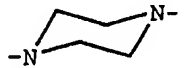
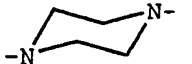
Ex. #	R ²	R ¹	L	B	E	P
90	Cl	CH ₂ OH	-NH-	H	H	H
91	CH ₂ OH	Cl	-NHCH ₂ CH ₂ -	H	H	COCH ₃
92	CH ₂ OH	Cl	-NHCH ₂ CH ₂ -	H	H	H
93	CH ₂ OH	Cl	-NHCH ₂ CH ₂ -	H	CH ₃	H
94	CH ₂ OH	Cl	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
95	CH ₂ OH	Cl	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
96	CH ₂ OH	Cl	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
97	CH ₂ OH	Cl	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
98	CH ₂ OH	Cl	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉ (n)
99	Cl	CH ₂ OH	-NHCH ₂ CH ₂ -	H	H	COCH ₃
100	Cl	CH ₂ OH	-NHCH ₂ CH ₂ -	H	H	H

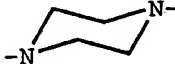
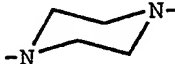
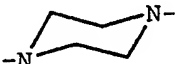
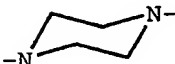
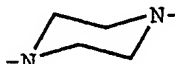
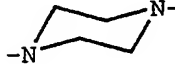
Ex. #	R ²	R ¹	L	B	E	P
101	CH ₂ OH	Cl		*	H	COCH ₃
102	CH ₂ OH	Cl		*	H	H
103	CH ₂ OH	Cl		*	CH ₃	H
104	CH ₂ OH	Cl		*	CH ₃	COCH ₃
105	CH ₂ OH	Cl		*	C ₂ H ₅	COCH ₃
106	CH ₂ OH	Cl		*	C ₂ H ₅	H
107	CH ₂ OH	Cl		*	H	COC ₄ H ₉ (n)
108	CH ₂ OH	Cl		*	H	COC ₄ H ₉ (n)


Ex. #	R ²	R ¹	L	B	E	P
109	Cl	CH ₂ OH		*	H	COCH ₃
110	Cl	CH ₂ OH		*	H	H
111	CH ₂ OCH ₃	Cl	-NH-	H	H	COCH ₃
112	CH ₂ OCH ₃	Cl	-NH-	H	H	H
113	Cl	CH ₂ OCH ₃	-NH-	H	H	COCH ₃
114	Cl	CH ₂ OCH ₃	-NH-	H	H	H
115	CH ₂ OH	CF ₃	-NH-	H	H	COCH ₃
116	CH ₂ OH	CF ₃	-NH-	H	H	H
117	CH ₂ OH	C ₂ F ₅	-NH-	H	H	COCH ₃
118	CH ₂ OH	C ₂ F ₅	-NH-	H	H	H
119	CH ₂ OH	C ₃ F ₇	-NH-	H	H	COCH ₃

Ex. #	R ²	R ¹	L	B	E	P
120	CH ₂ OH	C ₃ F ₇	-NH-	H	H	H
121	CHO	Cl	-NH-	H	H	COCH ₃
122	CHO	Cl	-NH-	H	H	H
123	Cl	CHO	-NH-	H	H	COCH ₃
124	Cl	CHO	-NH-	H	H	H
125	CO ₂ H	Cl	-NH-	H	H	COCH ₃
126	CO ₂ H	Cl	-NH-	H	H	COCH ₃
127	Cl	CO ₂ H	-NH-	H	H	COCH ₃
128	Cl	CO ₂ H	-NH-	H	H	H
129	CH ₂ OH	Br	-NH-	H	H	COCH ₃
130	CH ₂ OH	Br	-NH-	H	H	H

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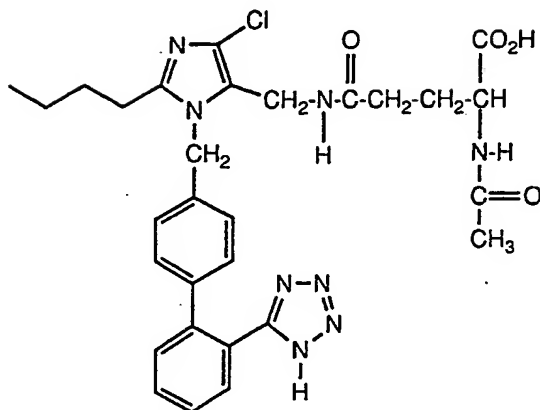
Ex. #	R ²	R ¹	L	B	E	P
131	Cl	CHO	-NHCH ₂ CH ₂ -	H	H	COCH ₃
132	Cl	CHO	-NHCH ₂ CH ₂ -	H	H	H
133	CO ₂ H	Cl	-NHCH ₂ CH ₂ -	H	H	COCH ₃
134	CO ₂ H	Cl	-NHCH ₂ CH ₂ -	H	H	H
135	Cl	CO ₂ H	-NHCH ₂ CH ₂ -	H	H	COCH ₃
136	Cl	CO ₂ H	-NHCH ₂ CH ₂ -	H	H	H
137	CH ₂ OH	Br	-NHCH ₂ CH ₂ -	H	H	COCH ₃
138	CH ₂ OH	Br	-NHCH ₂ CH ₂ -	H	H	H
139	Cl	CHO		*	H	COCH ₃
140	Cl	CHO		*	H	H

Ex. #	R ²	R ¹	L	B	E	P
141	CO ₂ H	Cl		*	H	COCH ₃
142	CO ₂ H	Cl		*	H	H
143	Cl	CO ₂ H		*	H	COCH ₃
144	Cl	CO ₂ H		*	H	H
145	CH ₂ OH	Br		*	H	COCH ₃
146	CH ₂ OH	Br		*	H	H

*  equals piperazinyl

Another class of highly preferred specific conjugates of the invention is provided by conjugates formed from a biphenylmethyl 1H-substituted imidazole AII antagonist compound having a terminal amino group attached to the imidazole nucleus. In this family of conjugates, the cleavable glutamyl residue is attached through an amide bond formed between the carbonyl at the gamma carbon of the glutamyl residue and the terminal amino nitrogen of the AII antagonist imidazole nucleus. Such conjugates are shown as Examples #147-#710. General procedures for preparation of the conjugates of Examples #147-#710 are described in Schemes IV-V. Detailed procedures for preparation of representative conjugates are described in Examples #147 and #148. Procedures similar to these aforementioned general and specific procedures may be used for preparation of the conjugates identified as Examples #149-#710 shown in Table VI.

Example 147



5 N2-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine

Step 1: Preparation of 5-aminomethyl-2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)biphenyl]-4-methyl]imidazole.

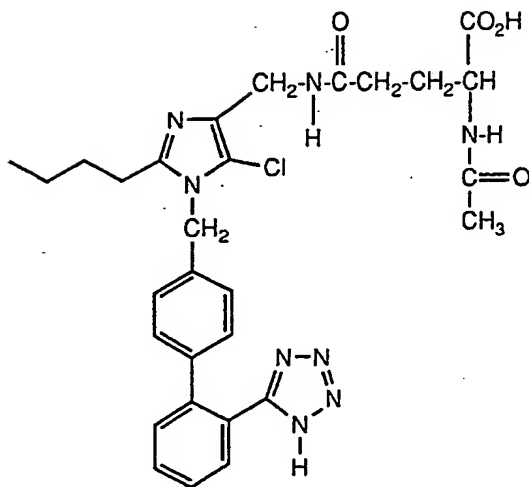
- 10 A solution of 4.20 g (10 mmol) of the compound of Example 80, 7.7 g (100 mmol) of ammonium acetate, and 439 mg (7 mmol) of NaBH₃CN in 30 mL of absolute methanol is stirred at ambient temperature for 48 h. Concentrated HCl is added until pH<2, and the methanol is removed in vacuo.
- 15 The residue is dissolved in water and is extracted with ethyl acetate. The aqueous solution is brought to pH>10 with 50% NaOH, is saturated with NaCl, and is extracted with methylene chloride. The extracts are combined, are dried (MgSO₄), and are evaporated in vacuo to give the
- 20 crude product. Purification by reverse phase chromatography (Waters DeltaPrep-3000) provides the pure 5-aminomethyl product.

Step 2: Preparation of N2-acetyl-N-[[2-butyl-4-chloro-1-
[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-
imidazol-5-yl]methyl]-L-glutamine

5

To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid- α -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The
10 reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of the 5-aminomethyl compound of step 1 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a
15 volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted
20 to 8 with 1 M K₂CO₃. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K₂CO₃ is added every 30 min for 5 h; the pH is maintained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to
25 warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Delta- prep-3000) gives the pure product.

Example 148



5 N2-acetyl-N-[[2-butyl-5-chloro-1-[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-imidazol-4-yl)methyl]-L-glutamine

Step 1: Preparation of 2-butyl-5-chloro-4-formyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl)imidazole.

10 A mixture of 2.11 g (5.0 mmol) of the compound of Example 79 and 3.08 g (35 mmol) of activated manganese dioxide in 30 mL of methylene chloride at ambient temperature is stirred for 40 h. The reaction mixture is filtered through celite, and the filtrate is concentrated
15 in vacuo. Purification by reverse phase chromatography provided the pure 4-formyl product.

Step 2: Preparation of 4-aminomethyl-2-butyl-5-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl)imidazole.

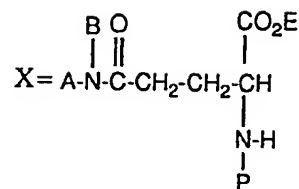
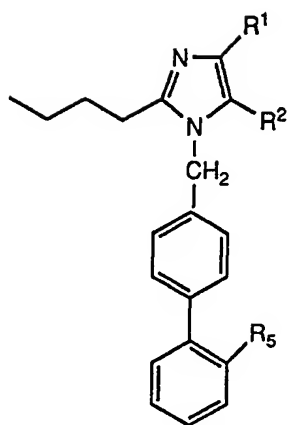
20 A solution of 4.20 g (10 mmol) of the aldehyde from step 1, 7.7 g (100 mmol) of ammonium acetate, and 439

mg (7 mmol) of NaBH_3CN in 30 mL of absolute methanol is stirred at ambient temperature for 48 h. Concentrated HCl is added until $\text{pH} < 2$, and the methanol is removed in vacuo. The residue is dissolved in water and is extracted with ethyl acetate. The aqueous solution is brought to $\text{pH} > 10$ with 50% NaOH , is saturated with NaCl , and is extracted with methylene chloride. The extracts are combined, are dried (MgSO_4), and are evaporated in vacuo to give the crude product. Purification by reverse phase chromatography (Waters Deltaprep-3000) provides the pure product.

Step 3: Preparation of N2-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)][1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl-L-glutamine

To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid- α -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of the 4-aminomethyl compound of step 2 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C , and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K_2CO_3 . The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K_2CO_3 is added every 30 min for 5 h; the pH is maintained at 9 and the reaction temperature is kept below

5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Delta-prep-3000) gives the pure product.

TABLE VI

Ex: #	R ¹	R ²	R ₅	A	B	E	P
149	Cl	X	CO ₂ H	single bond	H	H	COCH ₃
150	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
151	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
152	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
153	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
154	Cl	X	CN ₄ H	single bond	H	H	COCH ₃

Ex: #	R ¹	R ²	R ₅	A	B	E	P
155	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
156	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
157	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
158	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
159	Cl	X	CO ₂ H	single bond	H	H	H
160	Cl	X	CO ₂ H	single bond	H	CH ₃	H
161	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
162	Cl	X	CN ₄ H	single bond	H	H	H
163	Cl	X	CN ₄ H	single bond	H	CH ₃	H
164	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
165	Cl	X	CO ₂ H	-CH ₂ -	H	H	COCH ₃
166	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
167	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
168	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
169	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
170	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
171	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
172	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
173	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
174	Cl	X	CO ₂ H	-CH ₂ -	H	H	H
175	Cl	X	CO ₂ H	single bond	H	CH ₃	H
176	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
177	Cl	X	CN ₄ H	-CH ₂ -	H	H	H

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
178	Cl	X	CN ₄ H	single bond	H	CH ₃	H
179	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
180	Cl	X	CN ₄ H	-CH ₂ -	CH ₃	H	H
181	Cl	X	CN ₄ H	-CH ₂ -	CH ₃	H	COCH ₃
182	Cl	X	CO ₂ H	-CH ₂ CH ₂ -	H	H	COCH ₃
183	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
184	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
185	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
186	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
187	Cl	X	CN ₄ H	-CH ₂ CH ₂ -	H	H	COCH ₃
188	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
189	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
190	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
191	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
192	Cl	X	CO ₂ H	-CH ₂ CH ₂ -	H	H	H
193	Cl	X	CO ₂ H	single bond	H	CH ₃	H
194	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
195	Cl	X	CN ₄ H	-CH ₂ CH ₂ -	H	H	H
196	Cl	X	CN ₄ H	single bond	H	CH ₃	H
197	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
198	Cl	X	CO ₂ H	C ₃ H ₆ (n)	H	H	COCH ₃
199	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl

Ex: #	R ¹	R ²	R ₅	A	B	E	P
200	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
201	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
202	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
203	Cl	X	CN ₄ H	C ₃ H ₆ (n)	H	H	COCH ₃
204	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
205	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
206	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
207	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
208	Cl	X	CO ₂ H	C ₃ H ₆ (n)	H	H	H
209	Cl	X	CO ₂ H	single bond	H	CH ₃	H
210	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
211	Cl	X	CN ₄ H	C ₃ H ₆ (n)	H	H	H
212	Cl	X	CN ₄ H	single bond	H	CH ₃	H
213	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
214	Cl	X	CO ₂ H	C ₄ H ₈ (n)	H	H	COCH ₃
215	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
216	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
217	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
218	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
219	Cl	X	CN ₄ H	C ₄ H ₈ (n)	H	H	COCH ₃
220	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
221	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
222	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
223	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
224	Cl	X	CO ₂ H	C ₄ H ₈ (n)	H	H	H
225	Cl	X	CO ₂ H	single bond	H	CH ₃	H
226	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
227	Cl	X	CN ₄ H	C ₄ H ₈ (n)	H	H	H
228	Cl	X	CN ₄ H	single bond	H	CH ₃	H
229	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
230	Cl	X	CO ₂ H		H	H	COCH ₃
231	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
232	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉



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233	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
234	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
235	Cl	X	CN ₄ H		H	H	COCH ₃
236	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
237	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
238	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
239	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
240	Cl	X	CO ₂ H		H	H	H
241	Cl	X	CO ₂ H	single bond	H	CH ₃	H
242	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
243	Cl	X	CN ₄ H		H	H	H

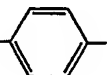
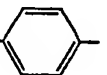

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244	Cl	X	CN ₄ H	single bond	H	CH ₃	H
245	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
246	Cl	X	CO ₂ H	-CH ₂ - 	H	H	COCH ₃
247	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
248	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
249	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
250	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
251	Cl	X	CN ₄ H	-CH ₂ - 	H	H	COCH ₃
252	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
253	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
254	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃

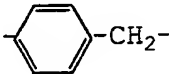
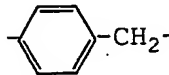
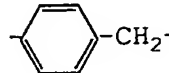
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256	Cl	X	CO ₂ H	-CH ₂ - 	H	H	H
257	Cl	X	CO ₂ H	single bond	H	CH ₃	H
258	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
259	Cl	X	CN ₄ H	-CH ₂ - 	H	H	H
260	Cl	X	CN ₄ H	single bond	H	CH ₃	H
261	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
262	Cl	X	CO ₂ H	 -CH ₂ -	H	H	COCH ₃
263	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
264	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉



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


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267	Cl	X	CN ₄ H		H	H	COCH ₃
268	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
269	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
270	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
271	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
272	Cl	X	CO ₂ H		H	H	H
273	Cl	X	CO ₂ H	single bond	H	CH ₃	H
274	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
275	Cl	X	CN ₄ H		H	H	H

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


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277	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
278	Cl	X	CO ₂ H	-CH ₂ -  -CH ₂ -	H	H	COCH ₃
279	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
280	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
281	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
282	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
283	Cl	X	CN ₄ H	-CH ₂ -  -CH ₂ -	H	H	COCH ₃
284	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
285	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
286	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
287	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
288	Cl	X	CO ₂ H	-CH ₂ -  -CH ₂ -	H	H	H
289	Cl	X	CO ₂ H	single bond	H	CH ₃	H
290	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
291	Cl	X	CN ₄ H	-CH ₂ -  -CH ₂ -	H	H	H
292	Cl	X	CN ₄ H	single bond	H	CH ₃	H
293	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
294	Cl	X	CN ₄ H	-CH ₂ CH ₂ -  -	H	H	COCH ₃
295	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
296	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
297	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃

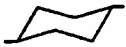
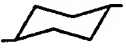
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Ex: #	R ¹	R ²	R ₅	A	B	E	P
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299	Cl	X	CN ₄ H	-CH ₂ CH ₂ - 	H	H	H
300	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
301	Cl	X	CN ₄ H	single bond	H	COC ₄ H ₉	
302	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
303	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
304	Cl	X	CN ₄ H	 -CH ₂ -CH ₂ -H	H	H	COCH ₃
305	Cl	X	CO ₂ H	single bond	H	CH ₃	H
306	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
307	Cl	X	CN ₄ H	 -CH ₂ -CH ₂ -H	H	H	H

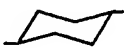
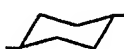
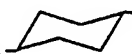
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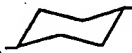
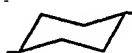
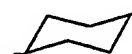
Ex: #	R ¹	R ²	R ₅	A	B	E	P
308	Cl	X	CN ₄ H	single bond	H	CH ₃	H
309	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
310	Cl	X	CO ₂ H		H	H	COCH ₃
311	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
312	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
313	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
314	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
315	Cl	X	CN ₄ H		H	H	COCH ₃
316	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
317	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
318	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
319	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
320	Cl	X	CO ₂ H		H	H	H
321	Cl	X	CO ₂ H	single bond	H	CH ₃	H
322	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
323	Cl	X	CN ₄ H		H	H	H
324	Cl	X	CN ₄ H	single bond	H	CH ₃	H
325	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
326	Cl	X	CO ₂ H	-CH ₂ - 	H	H	COCH ₃
327	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
328	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
329	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃



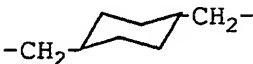
SUBSTITUTE SHEET

Ex: #	R ¹	R ²	R ₅	A	B	E	P
330	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
331	Cl	X	CN ₄ H	-CH ₂ - 	H	H	COCH ₃
332	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
333	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
334	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
335	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
336	Cl	X	CO ₂ H	-CH ₂ - 	H	H	H
337	Cl	X	CO ₂ H	single bond	H	CH ₃	H
338	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
339	Cl	X	CN ₄ H	-CH ₂ - 	H	H	H
340	Cl	X	CN ₄ H	single bond	H	CH ₃	H

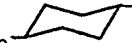


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Ex: #	R ¹	R ²	R ₅	A	B	E	P
341	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
342	Cl	X	CO ₂ H	 CH ₂ -	H	H	COCH ₃
343	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
344	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
345	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
346	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
347	Cl	X	CN ₄ H	 CH ₂ -	H	H	COCH ₃
348	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
349	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
350	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
351	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃

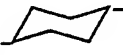
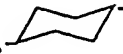
SUBSTITUTE SHEET

Ex: #	R ¹	R ²	R ₅	A	B	E	P
352	Cl	X	CO ₂ H		H	H	H
353	Cl	X	CO ₂ H	single bond	H	CH ₃	H
354	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
355	Cl	X	CN ₄ H		H	H	H
356	Cl	X	CN ₄ H	single bond	H	CH ₃	H
357	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
358	Cl	X	CO ₂ H		H	H	COCH ₃
359	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
360	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
361	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
362	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃

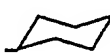
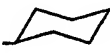
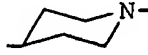
SUBSTITUTE SHEET

Ex: #	R ¹	R ²	R ₅	A	B	E	P
363	Cl	X	CN ₄ H	-CH ₂ -  -CH ₂ -	H	H	COCH ₃
364	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
365	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
366	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
367	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
368	Cl	X	CO ₂ H	-CH ₂ -  -CH ₂ -	H	H	H
369	Cl	X	CO ₂ H	single bond	H	CH ₃	H
370	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
371	Cl	X	CN ₄ H	-CH ₂ -  -CH ₂ -	H	H	H
372	Cl	X	CN ₄ H	single bond	H	CH ₃	H

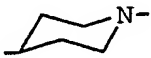


SUBSTITUTE SHEET

Ex: #	R ¹	R ²	R ₅	A	B	E	P
373	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
374	Cl	X	CN ₄ H	-CH ₂ CH ₂ - 	H	H	COCH ₃
375	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
376	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
377	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
378	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
379	Cl	X	CN ₄ H	-CH ₂ CH ₂ - 	H	H	H
380	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
381	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
382	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
383	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃

SUBSTITUTE SHEET


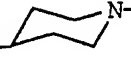
Ex: #	R ¹	R ²	R ₅	A	B	E	P
384	Cl	X	CN ₄ H	 CH ₂ CH ₂ -	H	H	COCH ₃
385	Cl	X	CO ₂ H	single bond	H	CH ₃	H
386	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
387	Cl	X	CN ₄ H	 CH ₂ CH ₂ -	H	H	H
388	Cl	X	CN ₄ H	single bond	H	CH ₃	H
389	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
390	Cl	X	CN ₄ H	 N-	*	H	COCH ₃
391	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
392	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
393	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
394	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃

SUBSTITUTE SHEET

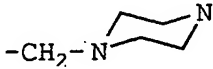
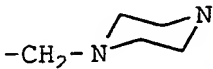
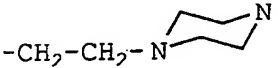
Ex: #	R ¹	R ²	R ₅	A	B	E	P
395	Cl	X	CN ₄ H		*	H	H
396	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
397	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
398	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
399	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
400	Cl	X	CN ₄ H		*	H	COCH ₃
401	Cl	X	CO ₂ H	single bond	H	CH ₃	H
402	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
403	Cl	X	CN ₄ H		*	H	H
404	Cl	X	CN ₄ H	single bond	H	CH ₃	H

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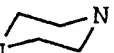
Ex: #	R ¹	R ²	R ₅	A	B	E	P
405	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
406	Cl	X	CN ₄ H	-CH ₂ CH ₂ - 	*	H	COCH ₃
407	Cl	X	CO ₂ H	single bond	H	H	COCH ₂ Cl
408	Cl	X	CO ₂ H	single bond	H	H	COC ₄ H ₉
409	Cl	X	CO ₂ H	single bond	H	CH ₃	COCH ₃
410	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
411	Cl	X	CN ₄ H	-CH ₂ -CH ₂ - 	*	H	H
412	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
413	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
414	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃
415	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃

SUBSTITUTE SHEET

Ex: #	R ¹	R ²	R ₅	A	B	E	P
416	Cl	X	CN ₄ H		*	H	COCH ₃
417	Cl	X	CO ₂ H	single bond	H	CH ₃	H
418	Cl	X	CO ₂ H	single bond	H	C ₂ H ₅	H
419	Cl	X	CN ₄ H		*	H	H
420	Cl	X	CN ₄ H	single bond	H	CH ₃	H
421	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
422	Cl	X	CN ₄ H		*	H	COCH ₃
423	Cl	X	CN ₄ H	single bond	H	H	COCH ₂ Cl
424	Cl	X	CN ₄ H	single bond	H	H	COC ₄ H ₉
425	Cl	X	CN ₄ H	single bond	H	CH ₃	COCH ₃

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
426	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
427	Cl	X	CN ₄ H	-CH ₂ CH ₂ -N  *	H	H	
428	Cl	X	CN ₄ H	single bond	H	CH ₃	H
429	Cl	X	CN ₄ H	single bond	H	C ₂ H ₅	H
430	X	Cl	CO ₂ H	single bond	H	H	COCH ₃
431	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
432	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
433	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
434	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
435	X	Cl	CN ₄ H	single bond	H	H	COCH ₃
436	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl

SUBSTITUTE SHEET

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
437	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
438	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
439	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
440	X	Cl	CO ₂ H	single bond	H	H	H
441	X	Cl	CO ₂ H	single bond	H	CH ₃	H
442	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
443	X	Cl	CN ₄ H	single bond	H	H	H
444	X	Cl	CN ₄ H	single bond	H	CH ₃	H
445	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
446	X	Cl	CO ₂ H	-CH ₂ -	H	H	COCH ₃
447	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl

SUBSTITUTE SHEET

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
448	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
449	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
450	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
451	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
452	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
453	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
454	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
455	X	Cl	CO ₂ H	-CH ₂ -	H	H	H
456	X	Cl	CO ₂ H	single bond	H	CH ₃	H
457	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
458	X	Cl	CN ₄ H	-CH ₂ -	H	H	H

SUBSTITUTE SHEET

Ex: #	R ¹	R ²	R ₅	A	B	E	P
459	X	Cl	CN ₄ H	single bond	H	CH ₃	H
460	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
461	X	Cl	CN ₄ H	-CH ₂ -	CH ₃	H	H
462	X	Cl	CN ₄ H	-CH ₂ -	CH ₃	H	COCH ₃
463	X	Cl	CO ₂ H	-CH ₂ CH ₂ -	H	H	COCH ₃
464	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
465	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
466	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
467	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
468	X	Cl	CN ₄ H	-CH ₂ CH ₂ -	H	H	COCH ₃
469	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
470	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
471	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
472	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
473	X	Cl	CO ₂ H	-CH ₂ CH ₂ -	H	H	H
474	X	Cl	CO ₂ H	single bond	H	CH ₃	H
475	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
476	X	Cl	CN ₄ H	-CH ₂ CH ₂ -	H	H	H
477	X	Cl	CN ₄ H	single bond	H	CH ₃	H
478	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
479	X	Cl	CO ₂ H	C ₃ H ₆ (n)	H	H	COCH ₃
480	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
481	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉

SUBSTITUTE SHEET

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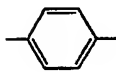
Ex: #	R ¹	R ²	R ₅	A	B	E	P
482	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
483	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
484	X	Cl	CN ₄ H	C ₃ H ₆ (n)	H	H	COCH ₃
485	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
486	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
487	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
488	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
489	X	Cl	CO ₂ H	C ₃ H ₆ (n)	H	H	H
490	X	Cl	CO ₂ H	single bond	H	CH ₃	H
491	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
492	X	Cl	CN ₄ H	C ₃ H ₆ (n)	H	H	H

SUBSTITUTE SHEET

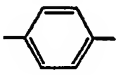
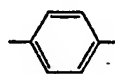

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
493	X	Cl	CN ₄ H	single bond	H	CH ₃	H
494	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
495	X	Cl	CO ₂ H	C ₄ H ₈ (n)	H	H	COCH ₃
496	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
497	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
498	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
499	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
500	X	Cl	CN ₄ H	C ₄ H ₈ (n)	H	H	COCH ₃
501	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
502	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
503	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃

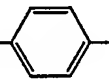
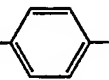
SUBSTITUTE SHEET

Ex: #	R ¹	R ²	R ₅	A	B	E	P
504	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
505	X	Cl	CO ₂ H	C ₄ H ₈ (n)	H	H	H
506	X	Cl	CO ₂ H	single bond	H	CH ₃	H
507	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
508	X	Cl	CN ₄ H	C ₄ H ₈ (n)	H	H	H
509	X	Cl	CN ₄ H	single bond	H	CH ₃	H
510	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
511	X	Cl	CO ₂ H		H	H	COCH ₃
512	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
513	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
514	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃


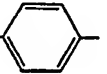

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
515	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
516	X	Cl	CN ₄ H		H	H	COCH ₃
517	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
518	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
519	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
520	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
521	X	Cl	CO ₂ H		H	H	H
522	X	Cl	CO ₂ H	single bond	H	CH ₃	H
523	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
524	X	Cl	CN ₄ H		H	H	H



SUBSTITUTE SHEET

Ex: #	R ¹	R ²	R ₅	A	B	E	P
525	X	Cl	CN ₄ H	single bond	H	CH ₃	H
526	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
527	X	Cl	CO ₂ H	-CH ₂ - 	H	H	COCH ₃
528	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
529	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
530	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
531	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
532	X	Cl	CN ₄ H	-CH ₂ - 	H	H	COCH ₃
533	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
534	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉

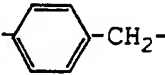

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
535	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
536	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
537	X	Cl	CO ₂ H	-CH ₂ - 	H	H	H
538	X	Cl	CO ₂ H	single bond	H	CH ₃	H
539	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
540	X	Cl	CN ₄ H	-CH ₂ - 	H	H	H
541	X	Cl	CN ₄ H	single bond	H	CH ₃	H
542	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
543	X	Cl	CO ₂ H	 -CH ₂ -	H	H	COCH ₃
544	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl




SUBSTITUTE SHEET

Ex: #	R ¹	R ²	R ₅	A	B	E	P
545	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
546	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
547	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
548	X	Cl	CN ₄ H	 -CH ₂ -	H	H	COCH ₃
549	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
550	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
551	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
552	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
553	X	Cl	CO ₂ H	 -CH ₂ -	H	H	H
554	X	Cl	CO ₂ H	single bond	H	CH ₃	H

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
Ex: #	R ¹	R ²	R ₅	A	B	E	P
555	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
556	X	Cl	CN ₄ H		H	H	H
557	X	Cl	CN ₄ H	single bond	H	CH ₃	H
558	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
559	X	Cl	CO ₂ H		H	H	COCH ₃
560	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
561	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
562	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
563	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
564	X	Cl	CN ₄ H	-CH ₂ -  -CH ₂ -	H	H	COCH ₃
565	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
566	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
567	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
568	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
569	X	Cl	CO ₂ H	-CH ₂ -  -CH ₂ -	H	H	H
570	X	Cl	CO ₂ H	single bond	H	CH ₃	H
571	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
572	X	Cl	CN ₄ H	-CH ₂ -  -CH ₂ -	H	H	H
573	X	Cl	CN ₄ H	single bond	H	CH ₃	H



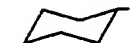
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Ex: #	R ¹	R ²	R ₅	A	B	E	P
574	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
575	X	Cl	CN ₄ H	-CH ₂ CH ₂ - 	H	H	COCH ₃
576	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
577	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
578	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
579	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
580	X	Cl	CN ₄ H	-CH ₂ CH ₂ - 	H	H	H
581	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
582	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
583	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃

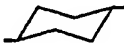


SUBSTITUTE SHEET

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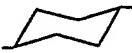
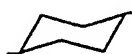
Ex: #	R ¹	R ²	R ₅	A	B	E	P
584	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
585	X	Cl	CN ₄ H	 -CH ₂ -CH ₂ -	H	H	COCH ₃
586	X	Cl	CO ₂ H	single bond	H	CH ₃	H
587	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
588	X	Cl	CN ₄ H	 -CH ₂ -CH ₂ -	H	H	H
589	X	Cl	CN ₄ H	single bond	H	CH ₃	H
590	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
591	X	Cl	CO ₂ H		H	H	COCH ₃
592	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
593	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉

SUBSTITUTE SHEET

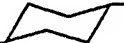
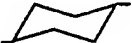

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
594	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
595	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
596	X	Cl	CN ₄ H		H	H	COCH ₃
597	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
598	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
599	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
600	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
601	X	Cl	CO ₂ H		H	H	H
602	X	Cl	CO ₂ H	single bond	H	CH ₃	H
603	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
604	X	Cl	CN ₄ H		H	H	H

SUBSTITUTE SHEET

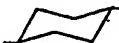
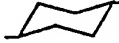
Ex: #	R ¹	R ²	R ₅	A	B	E	P
605	X	Cl	CN ₄ H	single bond	H	CH ₃	H
606	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
607	X	Cl	CO ₂ H	-CH ₂ - 	H	H	COCH ₃
608	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
609	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
610	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
611	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
612	X	Cl	CN ₄ H	-CH ₂ - 	H	H	COCH ₃
613	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
614	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
615	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃

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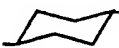
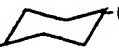

Ex: #	R ¹	R ²	R ₅	A	B	E	P
616	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
617	X	Cl	CO ₂ H	-CH ₂ - 	H	H	H
618	X	Cl	CO ₂ H	single bond	H	CH ₃	H
619	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
620	X	Cl	CN ₄ H	-CH ₂ - 	H	H	H
621	X	Cl	CN ₄ H	single bond	H	CH ₃	H
622	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
623	X	Cl	CO ₂ H	 -CH ₂ -	H	H	COCH ₃
624	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
625	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉

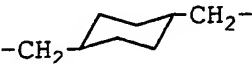

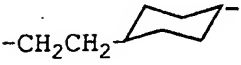
SUBSTITUTE SHEET

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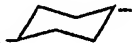

Ex: #	R ¹	R ²	R ₅	A	B	E	P
626	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
627	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
628	X	Cl	CN ₄ H	 CH ₂ -	H	H	COCH ₃
629	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
630	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
631	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
632	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
633	X	Cl	CO ₂ H	 CH ₂ -	H	H	H
634	X	Cl	CO ₂ H	single bond	H	CH ₃	H
635	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H

SUBSTITUTE SHEET

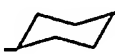
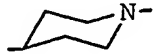
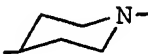
Ex: #	R ¹	R ²	R ₅	A	B	E	P
636	X	Cl	CN ₄ H	 CH ₂ -	H	H	H
637	X	Cl	CN ₄ H	single bond	H	CH ₃	H
638	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
639	X	Cl	CO ₂ H	-CH ₂ -  CH ₂ -	H	H	COCH ₃
640	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
641	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
642	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
643	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
644	X	Cl	CN ₄ H	-CH ₂ -  CH ₂ -	H	H	COCH ₃
645	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl

Ex: #	R ¹	R ²	R ₅	A	B	E	P
646	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
647	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
648	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
649	X	Cl	CO ₂ H		H	H	H
650	X	Cl	CO ₂ H	single bond	H	CH ₃	H
651	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
652	X	Cl	CN ₄ H		H	H	H
653	X	Cl	CN ₄ H	single bond	H	CH ₃	H
654	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
655	X	Cl	CN ₄ H		H	H	COCH ₃
656	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl

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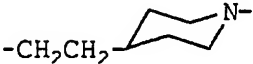
Ex: #	R ¹	R ²	R ₅	A	B	E	P
657	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
658	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
659	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
660	X	Cl	CN ₄ H	-CH ₂ CH ₂ - 	H	H	H
661	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
662	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
663	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
664	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
665	X	Cl	CN ₄ H	 CH ₂ CH ₂ -	H	H	COCH ₃
666	X	Cl	CO ₂ H	single bond	H	CH ₃	H

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
667	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
668	X	Cl	CN ₄ H	 CH ₂ CH ₂ -	H	H	H
669	X	Cl	CN ₄ H	single bond	H	CH ₃	H
670	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
671	X	Cl	CN ₄ H		*	H	COCH ₃
672	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
673	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
674	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
675	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
676	X	Cl	CN ₄ H		*	H	H
677	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl

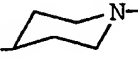
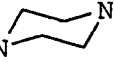
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Ex: #	R ¹	R ²	R ₅	A	B	E	P
678	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
679	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
680	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
681	X	Cl	CN ₄ H		*	H	COCH ₃
682	X	Cl	CO ₂ H	single bond	H	CH ₃	H
683	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
684	X	Cl	CN ₄ H		*	H	H
685	X	Cl	CN ₄ H	single bond	H	CH ₃	H
686	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
687	X	Cl	CN ₄ H		*	H	COCH ₃

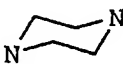
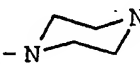
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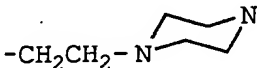
Ex: #	R ¹	R ²	R ₅	A	B	E	P
688	X	Cl	CO ₂ H	single bond	H	H	COCH ₂ Cl
689	X	Cl	CO ₂ H	single bond	H	H	COC ₄ H ₉
690	X	Cl	CO ₂ H	single bond	H	CH ₃	COCH ₃
691	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	COCH ₃
692	X	Cl	CN ₄ H-CH ₂ -CH ₂ - 	*	H	H	
693	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
694	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
695	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
696	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃
697	X	Cl	CN ₄ H-CH ₂ -N- 	*	H		COCH ₃

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Ex: #	R ¹	R ²	R ₅	A	B	E	P
698	X	Cl	CO ₂ H	single bond	H	CH ₃	H
699	X	Cl	CO ₂ H	single bond	H	C ₂ H ₅	H
700	X	Cl	CN ₄ H	-CH ₂ -N 	*	H	H
701	X	Cl	CN ₄ H	single bond	H	CH ₃	H
702	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H
703	X	Cl	CN ₄ H	-CH ₂ -CH ₂ -N 	*	H	COCH ₃
704	X	Cl	CN ₄ H	single bond	H	H	COCH ₂ Cl
705	X	Cl	CN ₄ H	single bond	H	H	COC ₄ H ₉
706	X	Cl	CN ₄ H	single bond	H	CH ₃	COCH ₃
707	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	COCH ₃

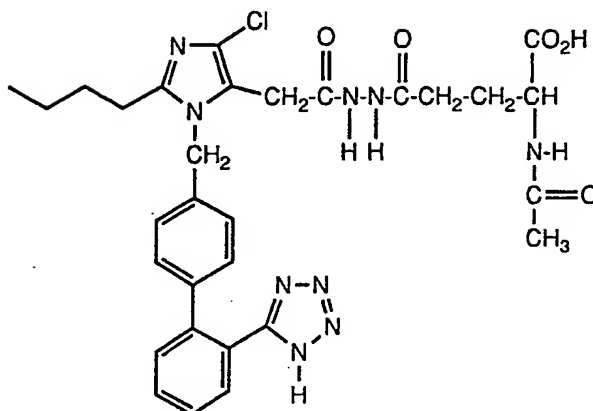
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Ex: #	R ¹	R ²	R ₅	A	B	E	P
708	X	Cl	CN ₄ H		*	H	H
709	X	Cl	CN ₄ H	single bond	H	CH ₃	H
710	X	Cl	CN ₄ H	single bond	H	C ₂ H ₅	H

*B is incorporated in A

Another class of highly preferred specific
conjugates of the invention is provided by conjugates
formed from a biphenylmethyl 1H-substituted imidazole AII
antagonist compound having a terminal carboxyl group
attached to the imidazo nucleus. In this family of
conjugates, the cleavable glutamyl residue is attached
through a diamino linker moiety which connects the imidazo
AII antagonist terminal carboxylic moiety through two amide
bonds to the gamma carbon of the glutamyl residue. Such
conjugates are shown as Examples 711-1526. General
procedures for preparation of the conjugates of Examples
#711-#1526 are described in Schemes VI-VII. Detailed
procedures for preparation of representative conjugates are
described in Examples #711 and #712. Procedures similar to
these aforementioned general and specific procedures may be
used for preparation of the conjugates identified as
Examples #711-#1526 shown in Table VII.

Example 711



N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide

Step 1: Preparation of 2-butyl-5-cyanomethyl-4-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl)-4-methyl]imidazole.

Thionyl chloride (7.2 mL, 98 mmol) is slowly dripped into a solution of 8.45 g (20.0 mmol) of the compound of Example 78 in a minimum of chloroform. The mixture is stirred for 2 h at ambient temperature and the solvent is removed in vacuo. The chloride is dissolved in dimethylsulfoxide (DMSO) and is added to a solution of 5.80 g (118 mmol) of sodium cyanide in 400 mL of DMSO. The solution is stirred overnight under nitrogen at ambient temperature; water is added and the aqueous layer is extracted with ethyl acetate. The extracts are combined, are dried (MgSO₄), and are concentrated in vacuo to give the crude product. Purification by silica gel chromatography (Waters DeltaPrep-500A) provides the pure 5-cyanomethyl derivative.

Step 2: Preparation of 2-butyl-5-carboxymethyl-4-chloro-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

5 A solution of 6.5 g (15 mmol) of the 5-cyanomethyl derivative from step 1 in 150 mL of concentrated hydrochloric acid/acetic acid (1:1) is stirred at reflux overnight. The solvents are removed in vacuo to give the crude product. Purification by reverse phase chromatography (Waters Deltaprep-3000) provides the pure 5-acetic acid derivative.

10

Step 3: Preparation of 2-butyl-4-chloro-5-methoxycarbonylmethyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

15 A solution of 4.5 g (10 mmol) of the 5-acetic acid derivative from step 2 in 150 mL of absolute methanol is cooled to -10°C and is treated with 1.5 mL (20 mmol) of thionyl chloride under nitrogen. The reaction is allowed to warm to ambient temperature and is stirred at reflux
20 overnight. The methanol is removed in vacuo and the crude product is dissolved in water. The pH is adjusted to pH 4 with 1N NaOH and the solution is extracted with ethyl acetate. The extracts are combined, are dried (MgSO₄), and are concentrated in vacuo to give the crude product. Purification
25 by silica gel chromatography (Waters Prep-500A) provides the pure 5-methyl acetate derivative.

Step 4: Preparation of 2-butyl-4-chloro-5-hydrazinylcarbonylmethyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

30

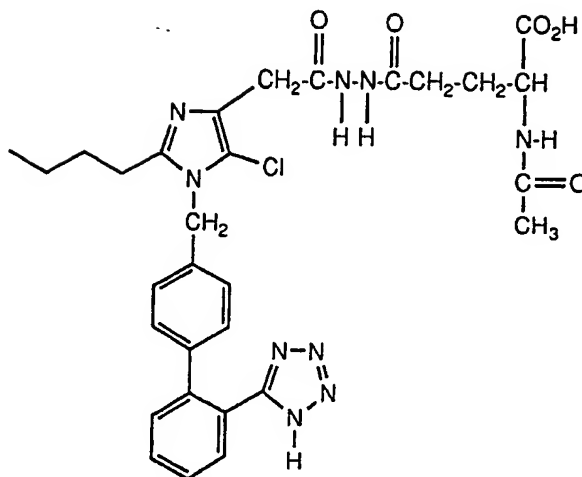
Under nitrogen, 2.32 g (5.0 mmol) of the 5-methyl acetate derivative from step 3 is dissolved in 50 mL of methanol and is treated with 5mL (160 mmol) of anhydrous hydrazine. The reaction is allowed to stir at reflux

overnight; concentration in vacuo gives the crude material. Purification by silica gel chromatography (Waters Prep-500A) provides the pure 5-acetic acid hydrazide derivative.

5 Step 5: Preparation of N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)][1,1'-biphenyl]-4-yl]methyl-1H-imidazol-5-yl]acetylhydrazide

10 To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid- α -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of
15 the hydrazide from step 4 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in
20 vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K₂CO₃. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K₂CO₃ is added every 30 min for 5 h; the pH is maintained at 9 and the
25 reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) gives the
30 pure product.

Example 712



5 N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[(2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl)methyl]-1H-imidazol-4-yl]acetylhydrazide

Step 1: Preparation of 2-butyl-4-cyanomethyl-5-chloro-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl]imidazole.

10 Thionyl chloride (7.2 mL, 98 mmol) is slowly dripped into a solution of 8.45 g (20.0 mmol) of the compound of Example 79 in a minimum of chloroform. The mixture is stirred for 2 h at ambient temperature and the solvent is removed in vacuo. The chloride is dissolved in DMSO and is
 15 added to a solution of 5.80 g (118 mmol) of sodium cyanide in 400 mL of DMSO. The solution is stirred overnight under nitrogen at ambient temperature; water is added and the aqueous layer is extracted with ethyl acetate. The extracts are combined, are dried (MgSO₄), and are concentrated in vacuo
 20 to give the crude product. Purification by silica gel chromatography (Waters Prep-500A) provides the pure 4-cyanomethyl derivative.

Step 2: Preparation of 2-butyl-4-carboxymethyl-5-chloro-1-
[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl)imidazole.

- 5 A solution of 6.5 g (15 mmol) of the 4-cyanomethyl
derivative from step 1 in 150 mL of concentrated hydrochloric
acid/acetic acid (1:1) is stirred at reflux overnight. The
solvents are removed in vacuo to give the crude product.
Purification by reverse phase chromatography provides (Waters
10 Deltaprep-3000) the pure 4-acetic acid derivative.

Step 3: Preparation of 2-butyl-5-chloro-4-methoxycarbonyl-
methyl-1-[(2'-(1H-tetrazol-5-yl)biphenyl-4-methyl)imidazole.

- 15 A solution of 4.5 g (10 mmol) of the 4-acetic acid
derivative from step 2 in 150 mL of absolute methanol is
cooled to -10°C and is treated with 1.5 mL (20 mmol) of
thionyl chloride under nitrogen. The reaction is allowed to
warm to ambient temperature and is stirred at reflux
20 overnight. The methanol is removed in vacuo and the crude
product is dissolved in water. The pH is adjusted to pH 4
with 1N NaOH and the solution is extracted with ethyl acetate.
The extracts are combined, are dried (MgSO₄), and are
concentrated in vacuo to give the crude product. Purification
25 by silica gel chromatography (Waters Prep-500A) provides the
pure 4-methyl acetate derivative.

Step 4: Preparation of 2-butyl-5-chloro-4-hydrazinylcarbonyl-
methyl-1-[(2'-(1H-tetrazole-5-yl)biphenyl-4-methyl)imidazole.

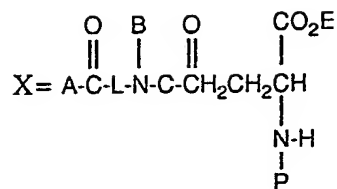
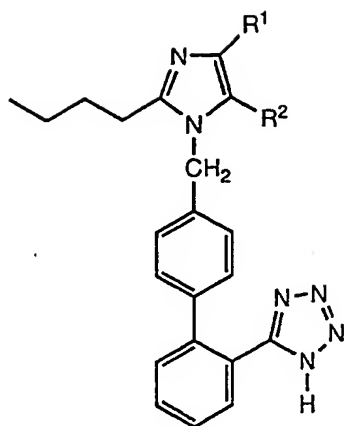
- 30 Under nitrogen, 2.32 g (5.0 mmol) of the 4-methyl
acetate derivative from step 3 is dissolved in 50 mL of
methanol and is treated with 5 mL (160 mmol) of anhydrous
hydrazine. The reaction is allowed to stir at reflux

overnight; concentration in vacuo gives the crude material. Purification by silica gel chromatography (Waters Prep-500A) provides the pure 4-acetic acid hydrazide derivative.

5 Step 5: Preparation of N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)][1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide



To a solution of 1.70 g (5.6 mmol) of N-Boc-L-glutamic acid- α -tertbutyl ester (BACHEM) in 50 mL of methylene chloride under nitrogen is added 580 mg (2.8 mmol) of solid dicyclohexylcarbodiimide (DCC). The reaction is allowed to stir for 2 h and is filtered under nitrogen. The anhydride solution is then added to a solution of 1.01 g (2.4 mmol) of the hydrazide from step 4 in 75 mL of methylene chloride under nitrogen. The reaction is stirred overnight, is concentrated to a volume of 25 mL, is cooled to 0°C, and is treated with 25 mL of TFA under nitrogen. The stirred reaction is allowed to warm to ambient temperature overnight and is concentrated in vacuo. The crude product is dissolved in 100 mL of acetonitrile/water (1:1) and the pH is adjusted to 8 with 1 M K₂CO₃. The solution is cooled to 0°C and 0.23 mL (2.4 mmol) of acetic anhydride and 2.4 mL (2.4 mmol) of 1 M K₂CO₃ is added every 30 min for 5 h; the pH is maintained at 9 and the reaction temperature is kept below 5°C. After the last addition, the reaction is allowed to warm to ambient temperature overnight. The pH is adjusted to 4 with 3 M HCl and the reaction is concentrated to 100 mL. Purification by reverse phase chromatography (Waters Deltaprep-3000) gives the pure product.

TABLE VII

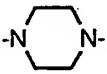
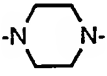
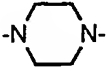
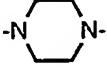
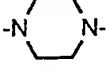
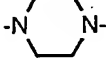


Ex. #	R ¹	R ²	A	L	B	E	P
713	Cl	X	single bond	-NH-	H	H	COCH ₃
714	Cl	X	single bond	-NH-	H	H	COCH ₂ Cl
715	Cl	X	single bond	-NH-	H	H	COC ₄ H ₉
716	Cl	X	single bond	-NH-	H	CH ₃	COCH ₃
717	Cl	X	single bond	-NH-	H	C ₂ H ₅	COCH ₃
718	Cl	X	single bond	-NH-	H	H	H
719	Cl	X	single bond	-NH-	H	CH ₃	H
720	Cl	X	single bond	-NH-	H	C ₂ H ₅	H

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Ex. #	R ¹	R ²	A	L	B	E	P
721	Cl	X	single bond	-NHCH ₂ CH ₂ -	H	H	COCH ₃
722	Cl	X	single bond	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
723	Cl	X	single bond	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
724	Cl	X	single bond	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
725	Cl	X	single bond	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
726	Cl	X	single bond	-NHCH ₂ CH ₂ -	H	H	H
727	Cl	X	single bond	-NHCH ₂ CH ₂ -	H	CH ₃	H
728	Cl	X	single bond	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
729	Cl	X	single bond		*	H	COCH ₃
730	Cl	X	single bond		H	H	COCH ₂ Cl

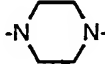
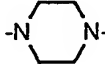

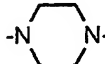
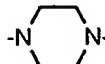
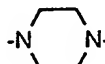
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Ex. #	R ¹	R ²	A	L	B	E	P
731	Cl	X	single bond		H	H	COC ₄ H ₉
732	Cl	X	single bond		H	CH ₃	COCH ₃
733	Cl	X	single bond		H	C ₂ H ₅	COCH ₃
734	Cl	X	single bond		*	H	H
735	Cl	X	single bond		H	CH ₃	H
736	Cl	X	single bond		H	C ₂ H ₅	H
737	Cl	X	CH ₂	-NH-	H	H	COCH ₂ Cl
738	Cl	X	CH ₂	-NH-	H	H	COC ₄ H ₉

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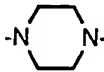
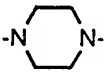
Ex. #	R ¹	R ²	A	L	B E	P
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740	Cl	X	CH ₂	-NH-	H C ₂ H ₅	COCH ₃
741	Cl	X	CH ₂	-NH-	H H	H
742	Cl	X	CH ₂	-NH-	H CH ₃	H
743	Cl	X	CH ₂	-NH-	H C ₂ H ₅	H
744	Cl	X	CH ₂	-NHCH ₂ CH ₂ -	H H	COCH ₃
745	Cl	X	CH ₂	-NHCH ₂ CH ₂ -	H H	COCH ₂ Cl
746	Cl	X	CH ₂	-NHCH ₂ CH ₂ -	H H	COC ₄ H ₉
747	Cl	X	CH ₂	-NHCH ₂ CH ₂ -	H CH ₃	COCH ₃
748	Cl	X	CH ₂	-NHCH ₂ CH ₂ -	H C ₂ H ₅	COCH ₃
749	Cl	X	CH ₂	-NHCH ₂ CH ₂ -	H H	H

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Ex. #	R ¹	R ²	A	L	B	E	P
750	Cl	X	CH ₂	-NHCH ₂ CH ₂ -	H	CH ₃	H
751	Cl	X	CH ₂	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
752	Cl	X	CH ₂		*	H	COCH ₃
753	Cl	X	CH ₂		H	H	COCH ₂ Cl
754	Cl	X	CH ₂		H	H	COC ₄ H ₉
755	Cl	X	CH ₂		H	CH ₃	COCH ₃
756	Cl	X	CH ₂		H	C ₂ H ₅	COCH ₃
757	Cl	X	CH ₂		*	H	H

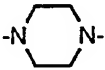
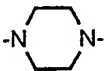
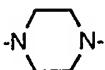
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Ex. #	R ¹	R ²	A	L	B E	P
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759	Cl	X	CH ₂		H C ₂ H ₅	H
760	Cl	X	CH ₂ CH ₂	-NH-	H H	COCH ₃
761	Cl	X	CH ₂ CH ₂	-NH-	H H	COCH ₂ Cl
762	Cl	X	CH ₂ CH ₂	-NH-	H H	COC ₄ H ₉
763	Cl	X	CH ₂ CH ₂	-NH-	H CH ₃	COCH ₃
764	Cl	X	CH ₂ CH ₂	-NH-	H C ₂ H ₅	COCH ₃
765	Cl	X	CH ₂ CH ₂	-NH-	H H	H
766	Cl	X	CH ₂ CH ₂	-NH-	H CH ₃	H
767	Cl	X	CH ₂ CH ₂	-NH-	H C ₂ H ₅	H
768	Cl	X	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H H	COCH ₃

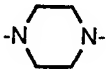
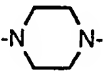
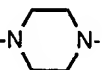
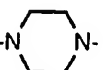
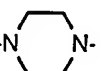
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Ex. #	R ¹	R ²	A	L	B	E	P
769	Cl	X	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
770	Cl	X	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
771	Cl	X	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
772	Cl	X	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
773	Cl	X	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	H	H
774	Cl	X	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	CH ₃	H
775	Cl	X	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
776	Cl	X	CH ₂ CH ₂		*	H	COCH ₃
777	Cl	X	CH ₂ CH ₂		H	H	COCH ₂ Cl
778	Cl	X	CH ₂ CH ₂		H	H	COC ₄ H ₉

SUBSTITUTE SHEET

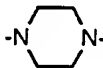
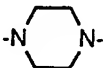
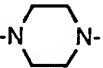
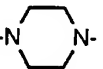
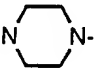
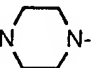
173

Ex. #	R ¹	R ²	A	L	B E	P
779	Cl	X	CH ₂ CH ₂		H CH ₃	COCH ₃
780	Cl	X	CH ₂ CH ₂		H C ₂ H ₅	COCH ₃
781	Cl	X	CH ₂ CH ₂		* H	H
782	Cl	X	CH ₂ CH ₂		H CH ₃	H
783	Cl	X	CH ₂ CH ₂		H C ₂ H ₅	H
784	Cl	X	C ₃ H ₆ (n)	-NH-	H H	COCH ₃
785	Cl	X	C ₃ H ₆ (n)	-NH-	H H	COCH ₂ Cl
786	Cl	X	C ₃ H ₆ (n)	-NH-	H H	COC ₄ H ₉



SUBSTITUTE SHEET

Ex. #	R ¹	R ²	A	L	B E	P
787	Cl	X	C ₃ H ₆ (n)	-NH-	H CH ₃	COCH ₃
788	Cl	X	C ₃ H ₆ (n)	-NH-	H C ₂ H ₅	COCH ₃
789	Cl	X	C ₃ H ₆ (n)	-NH-	H H	H
790	Cl	X	C ₃ H ₆ (n)	-NH-	H CH ₃	H
791	Cl	X	C ₃ H ₆ (n)	-NH-	H C ₂ H ₅	H
792	Cl	X	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H H	COCH ₃
793	Cl	X	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H H	COCH ₂ Cl
794	Cl	X	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H H	COC ₄ H ₉
795	Cl	X	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H CH ₃	COCH ₃
796	Cl	X	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H C ₂ H ₅	COCH ₃
797	Cl	X	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H H	H

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

Ex. #	R ¹	R ²	A	L	B	E	P
798	Cl	X	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H	CH ₃	H
799	Cl	X	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
800	Cl	X	C ₃ H ₆ (n)		*	H	COCH ₃
801	Cl	X	C ₃ H ₆ (n)		H	H	COCH ₂ Cl
802	Cl	X	C ₃ H ₆ (n)		H	H	COC ₄ H ₉
803	Cl	X	C ₃ H ₆ (n)		H	CH ₃	COCH ₃
804	Cl	X	C ₃ H ₆ (n)		H	C ₂ H ₅	COCH ₃
805	Cl	X	C ₃ H ₆ (n)		*	H	H

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Ex. #	R ¹	R ²	A	L	B E	P
806	Cl	X	C ₃ H ₆ (n)		H CH ₃	H
807	Cl	X	C ₃ H ₆ (n)		H C ₂ H ₅	H
808	Cl	X	C ₄ H ₈ (n)	-NH-	H H	COCH ₃
809	Cl	X	C ₄ H ₈ (n)	-NH-	H H	COCH ₂ Cl
810	Cl	X	C ₄ H ₈ (n)	-NH-	H H	COC ₄ H ₉
811	Cl	X	C ₄ H ₈ (n)	-NH-	H CH ₃	COCH ₃
812	Cl	X	C ₄ H ₈ (n)	-NH-	H C ₂ H ₅	COCH ₃
813	Cl	X	C ₄ H ₈ (n)	-NH-	H H	H
814	Cl	X	C ₄ H ₈ (n)	-NH-	H CH ₃	H
815	Cl	X	C ₄ H ₈ (n)	-NH-	H C ₂ H ₅	H
816	Cl	X	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H H	COCH ₃


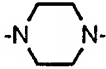
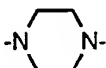
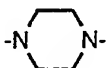
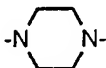
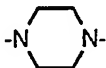

SUBSTITUTE SHEET

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Ex. #	R ¹	R ²	A	L	B	E	P
817	Cl	X	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
818	Cl	X	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
819	Cl	X	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
820	Cl	X	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
821	Cl	X	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	H	H
822	Cl	X	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	CH ₃	H
823	Cl	X	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
824	Cl	X	C ₄ H ₈ (n)		*	H	COCH ₃
825	Cl	X	C ₄ H ₈ (n)		H	H	COCH ₂ Cl



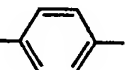
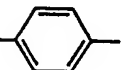
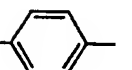
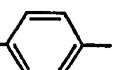
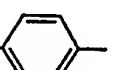
SUBSTITUTE SHEET

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Ex. #	R ¹	R ²	A	L	B E	P
826	Cl	X	C ₄ H ₈ (n)		H H	COC ₄ H ₉
827	Cl	X	C ₄ H ₈ (n)		H CH ₃	COCH ₃
828	Cl	X	C ₄ H ₈ (n)		H C ₂ H ₅	COCH ₃
829	Cl	X	C ₄ H ₈ (n)		* H	H
830	Cl	X	C ₄ H ₈ (n)		H CH ₃	H
831	Cl	X	C ₄ H ₈ (n)		H C ₂ H ₅	H
832	Cl	X		-NH-	H H	COCH ₃

SUBSTITUTE SHEET






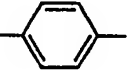

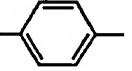

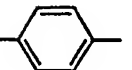

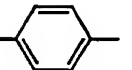

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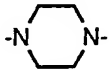


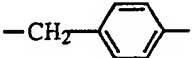
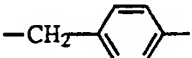
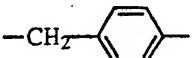
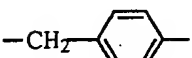
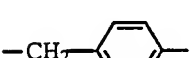
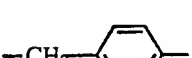
Ex. #	R ¹	R ²	A	L	B E	P
833	Cl	X		-NH-	H H	COCH ₂ Cl
834	Cl	X		-NH-	H H	COC ₄ H ₉
835	Cl	X		-NH-	H CH ₃	COCH ₃
836	Cl	X		-NH-	H C ₂ H ₅	COCH ₃
837	Cl	X		-NH-	H H	H
838	Cl	X		-NH-	H CH ₃	H
839	Cl	X		-NH-	H C ₂ H ₅	H

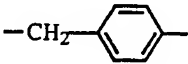
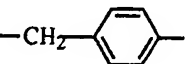
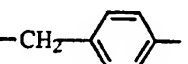
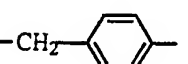
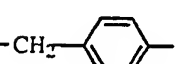
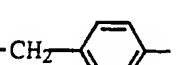
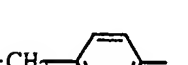
SUBSTITUTE SHEET

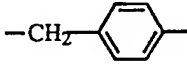
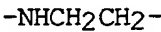
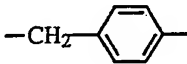
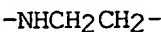
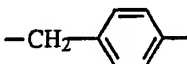
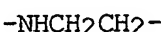
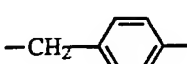
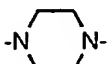
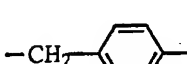
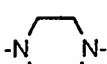

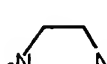


Ex. #	R ¹	R ²	A	L	B	E	P
840	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₃
841	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
842	Cl	X		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
843	Cl	X		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
844	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
845	Cl	X		-NHCH ₂ CH ₂ -	H	H	H
846	Cl	X		-NHCH ₂ CH ₂ -	H	CH ₃	H

SUBSTITUTE SHEET

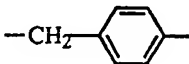

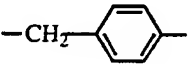

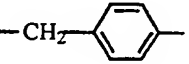

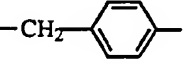
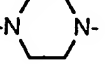
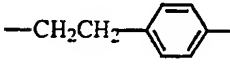
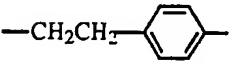
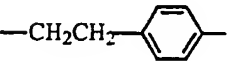
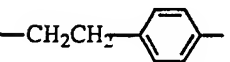
Ex. #	R ¹	R ²	A	L	B	E	P
847	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
848	Cl	X			*	H	COCH ₃
849	Cl	X			H	H	COCH ₂ Cl
850	Cl	X			H	H	COC ₄ H ₉
851	Cl	X			H	CH ₃	COCH ₃
852	Cl	X			H	C ₂ H ₅	COCH ₃
853	Cl	X			*	H	H

Ex. #	R ¹	R ²	A	L	B	E	P
854	Cl	X			H	CH ₃	H
855	Cl	X			H	C ₂ H ₅	H
856	Cl	X		-NH-	H	H	COCH ₃
857	Cl	X		-NH-	H	H	COCH ₂ Cl
858	Cl	X		-NH-	H	H	COC ₄ H ₉
859	Cl	X		-NH-	H	CH ₃	COCH ₃
860	Cl	X		-NH-	H	C ₂ H ₅	COCH ₃
861	Cl	X		-NH-	H	H	H





Ex. #	R ¹	R ²	A	L	B	E	P
862	Cl	X		-NH-	H	CH ₃	H
863	Cl	X		-NH-	H	C ₂ H ₅	H
864	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₃
865	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
866	Cl	X		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
867	Cl	X		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
868	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃









Ex. #	R ¹	R ²	A	L	B	E	P
869	Cl	X			H	H	H
870	Cl	X			H	CH ₃	H
871	Cl	X			H	C ₂ H ₅	H
872	Cl	X			*	H	COCH ₃
873	Cl	X			H	H	COCH ₂ Cl
874	Cl	X			H	H	COC ₄ H ₉
875	Cl	X			H	CH ₃	COCH ₃

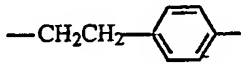

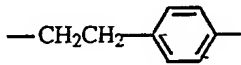
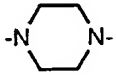
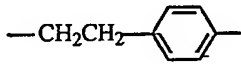
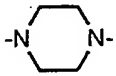
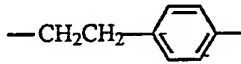
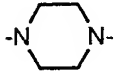
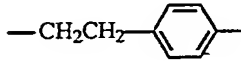

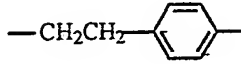

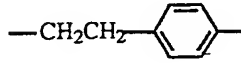

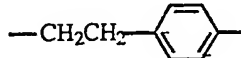
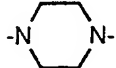
185

Ex. #	R ¹	R ²	A	L	B	E	P
876	Cl	X			H	C ₂ H ₅	COCH ₃
877	Cl	X			*	H	H
878	Cl	X			H	CH ₃	H
879	Cl	X			H	C ₂ H ₅	H
880	Cl	X		-NH-	H	H	COCH ₃
881	Cl	X		-NH-	H	H	COCH ₂ Cl
882	Cl	X		-NH-	H	H	COC ₄ H ₉
883	Cl	X		-NH-	H	CH ₃	COCH ₃

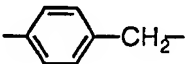
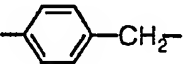
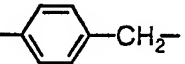
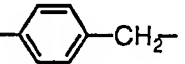
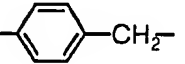
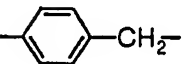
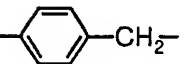
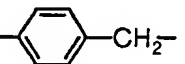
SUBSTITUTE SHEET

Ex. #	R ¹	R ²	A	L	B	E	P
884	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	C ₂ H ₅	COCH ₃
885	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	H	H
886	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	CH ₃	H
887	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	C ₂ H ₅	H

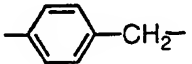
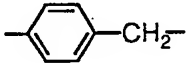
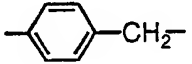
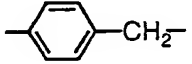
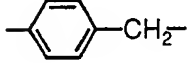
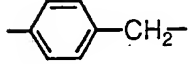
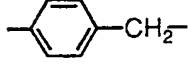
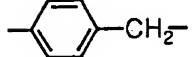
Ex.#	R ¹	R ²	A	L	B	E	P
888	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NHCH}_2\text{CH}_2-$	H	H	COCH ₃
889	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NHCH}_2\text{CH}_2-$	H	H	COCH ₂ Cl
890	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NHCH}_2\text{CH}_2-$	H	H	COC ₄ H ₉
891	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NHCH}_2\text{CH}_2-$	H	CH ₃	COCH ₃
892	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NHCH}_2\text{CH}_2-$	H	C ₂ H ₅	COCH ₃
893	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NHCH}_2\text{CH}_2-$	H	H	H
894	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NHCH}_2\text{CH}_2-$	H	CH ₃	H
895	Cl	X	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NHCH}_2\text{CH}_2-$	H	C ₂ H ₅	H

Ex.#	R ¹	R ²	A	L	B	E	P
896	Cl	X			*	H	COCH ₃
897	Cl	X			H	H	COCH ₂ Cl
898	Cl	X			H	H	COC ₄ H ₉
899	Cl	X			H	CH ₃	COCH ₃
900	Cl	X			H	C ₂ H ₅	COCH ₃
901	Cl	X			*	H	H
902	Cl	X			H	CH ₃	H
903	Cl	X			H	C ₂ H ₅	H

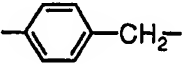

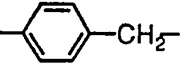

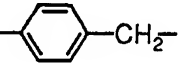
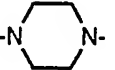
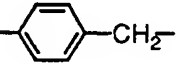

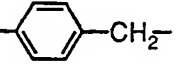
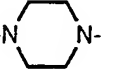
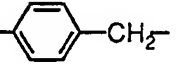
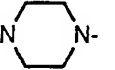
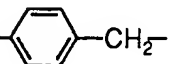
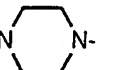
SUBSTITUTE SHEET

Ex.#	R ¹	R ²	A	L	B	E	P
904	Cl	X		-NH-	H	H	COCH ₃
905	Cl	X		-NH-	H	H	COCH ₂ Cl
906	Cl	X		-NH-	H	H	COC ₄ H ₉
907	Cl	X		-NH-	H	CH ₃	COCH ₃
908	Cl	X		-NH-	H	C ₂ H ₅	COCH ₃
909	Cl	X		-NH-	H	H	H
910	Cl	X		-NH-	H	CH ₃	H
911	Cl	X		-NH-	H	C ₂ H ₅	H

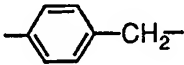
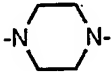
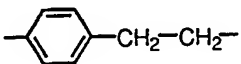
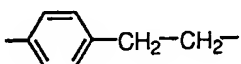
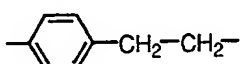
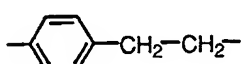
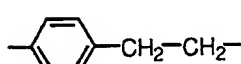
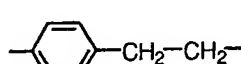
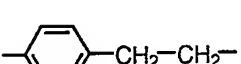
SUBSTITUTE SHEET









Ex.#	R ¹	R ²	A	L	B	E	P
912	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₃
913	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
914	Cl	X		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
915	Cl	X		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
916	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
917	Cl	X		-NHCH ₂ CH ₂ -	H	H	H
918	Cl	X		-NHCH ₂ CH ₂ -	H	CH ₃	H
919	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H



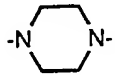

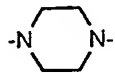

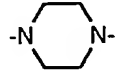

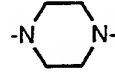

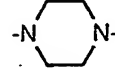

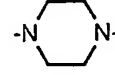

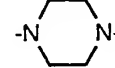
SUBSTITUTE SHEET

Ex.#	R ¹	R ²	A	L	B	E	P
920	Cl	X			*	H	COCH ₃
921	Cl	X			H	H	COCH ₂ Cl
922	Cl	X			H	H	COC ₄ H ₉
923	Cl	X			H	CH ₃	COCH ₃
924	Cl	X			H	C ₂ H ₅	COCH ₃
925	Cl	X			*	H	H
926	Cl	X			H	CH ₃	H


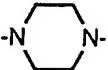







SUBSTITUTE SHEET

Ex.#	R ¹	R ²	A	L	B	E	P
927	Cl	X			H	C ₂ H ₅	H
928	Cl	X		-NH-	H	H	COCH ₃
929	Cl	X		-NH-	H	H	COCH ₂ Cl
930	Cl	X		-NH-	H	H	COC ₄ H ₉
931	Cl	X		-NH-	H	CH ₃	COCH ₃
932	Cl	X		-NH-	H	C ₂ H ₅	COCH ₃
933	Cl	X		-NH-	H	H	H
934	Cl	X		-NH-	H	CH ₃	H

Ex.#	R ¹	R ²	A	L	B	E	P
935	Cl	X	 -CH ₂ -CH ₂ -	-NH-	H	C ₂ H ₅	H
936	Cl	X	 -CH ₂ -CH ₂ -	-NHCH ₂ CH ₂ -	H	H	COCH ₃
937	Cl	X	 -CH ₂ -CH ₂ -	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
938	Cl	X	 -CH ₂ -CH ₂ -	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
939	Cl	X	 -CH ₂ -CH ₂ -	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
940	Cl	X	 -CH ₂ -CH ₂ -	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
941	Cl	X	 -CH ₂ -CH ₂ -	-NHCH ₂ CH ₂ -	H	H	H
942	Cl	X	 -CH ₂ -CH ₂ -	-NHCH ₂ CH ₂ -	H	CH ₃	H

Ex.#	R ¹	R ²	A	L	B	E	P
943	Cl	X	 -CH ₂ -CH ₂ -	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
944	Cl	X	 -CH ₂ -CH ₂ -		*	H	COCH ₃
945	Cl	X	 -CH ₂ -CH ₂ -		H	H	COCH ₂ Cl
946	Cl	X	 -CH ₂ -CH ₂ -		H	H	COC ₄ H ₉
947	Cl	X	 -CH ₂ -CH ₂ -		H	CH ₃	COCH ₃
948	Cl	X	 -CH ₂ -CH ₂ -		H	C ₂ H ₅	COCH ₃
949	Cl	X	 -CH ₂ -CH ₂ -		*	H	H
950	Cl	X	 -CH ₂ -CH ₂ -		H	CH ₃	H

SUBSTITUTE SHEET


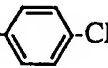
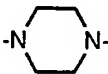
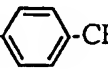
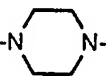
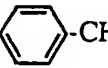
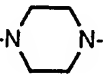
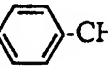
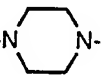
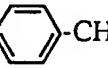
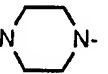
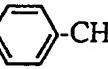
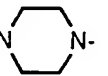
Ex.#	R ¹	R ²	A	L	B	E	P
951	Cl	X	 -CH ₂ -CH ₂ -		H	C ₂ H ₅	H
952	Cl	X	-CH ₂ -  -CH ₂ -	-NH-	H	H	COCH ₃
953	Cl	X	-CH ₂ -  -CH ₂ -	-NH-	H	H	COCH ₂ Cl
954	Cl	X	-CH ₂ -  -CH ₂ -	-NH-	H	H	COC ₄ H ₉
955	Cl	X	-CH ₂ -  -CH ₂ -	-NH-	H	CH ₃	COCH ₃
956	Cl	X	-CH ₂ -  -CH ₂ -	-NH-	H	C ₂ H ₅	COCH ₃
957	Cl	X	-CH ₂ -  -CH ₂ -	-NH-	H	H	H
958	Cl	X	-CH ₂ -  -CH ₂ -	-NH-	H	CH ₃	H

SUBSTITUTE SHEET


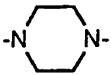

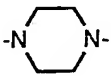
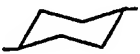
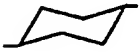
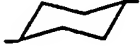
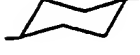
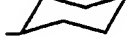
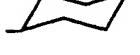

Ex.#	R ¹	R ²	A	L	B	E	P
959	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NH}-$	H	C ₂ H ₅	H
960	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	COCH ₃
961	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	COCH ₂ Cl
962	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	COC ₄ H ₉
963	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	CH ₃	COCH ₃
964	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	C ₂ H ₅	COCH ₃
965	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	H
966	Cl	X	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	CH ₃	H

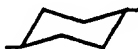
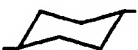
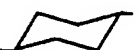





SUBSTITUTE SHEET

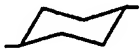
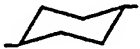
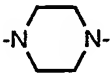
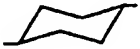
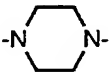
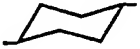
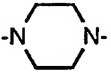
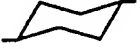
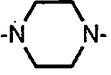
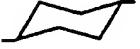
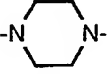
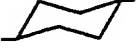
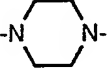


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Ex.#	R ¹	R ²	A	L	B	E	P
967	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
968	Cl	X			*	H	COCH ₃
969	Cl	X			H	H	COCH ₂ Cl
970	Cl	X			H	H	COC ₄ H ₉
971	Cl	X			H	CH ₃	COCH ₃
972	Cl	X			H	C ₂ H ₅	COCH ₃
973	Cl	X			*	H	H

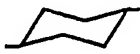
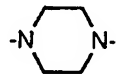







SUBSTITUTE SHEET

Ex.#	R ¹	R ²	A	L	B	E	P
974	Cl	X			H	CH ₃	H
975	Cl	X			H	C ₂ H ₅	H
976	Cl	X		-NH-	H	H	COCH ₃
977	Cl	X		-NH-	H	H	COCH ₂ Cl
978	Cl	X		-NH-	H	H	COC ₄ H ₉
979	Cl	X		-NH-	H	CH ₃	COCH ₃
980	Cl	X		-NH-	H	C ₂ H ₅	COCH ₃
981	Cl	X		-NH-	H	H	H
982	Cl	X		-NH-	H	CH ₃	H









Ex.#	R ¹	R ²	A	L	B	E	P
983	Cl	X		-NH-	H	C ₂ H ₅	H
984	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₃
985	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
986	Cl	X		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
987	Cl	X		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
988	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
989	Cl	X		-NHCH ₂ CH ₂ -	H	H	H
990	Cl	X		-NHCH ₂ CH ₂ -	H	CH ₃	H









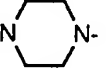
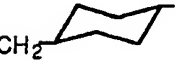
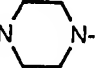
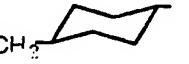
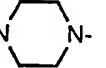
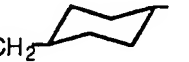
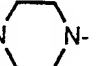
Ex.#	R ¹	R ²	A	L	B	E	P
991	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
992	Cl	X			*	H	COCH ₃
993	Cl	X			H	H	COCH ₂ Cl
994	Cl	X			H	H	COC ₄ H ₉
995	Cl	X			H	CH ₃	COCH ₃
996	Cl	X			H	C ₂ H ₅	COCH ₃
997	Cl	X			*	H	H
998	Cl	X			H	CH ₃	H

201


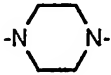
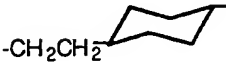
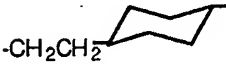
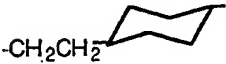
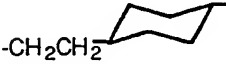
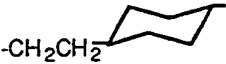
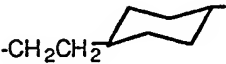
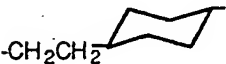
Ex.#	R ¹	R ²	A	L	B	E	P
999	Cl	X			H	C ₂ H ₅	H
1000		Cl		X		-NH-	H
1001		Cl		X		-NH-	H
1002	Cl	X		-NH-	H	H	COC ₄ H ₉
1003	Cl	X		-NH-	H	CH ₃	COCH ₃
1004	Cl	X		-NH-	H	C ₂ H ₅	COCH ₃
1005	Cl	X		-NH-	H	H	H
1006	Cl	X		-NH-	H	CH ₃	H










SUBSTITUTE SHEET

Ex.#	R ¹	R ²	A	L	B	E	P
1007	Cl	X		-NH-	H	C ₂ H ₅	H
1008	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₃
1009	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1010	Cl	X		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1011	Cl	X		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1012	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1013	Cl	X		-NHCH ₂ CH ₂ -	H	H	H
1014	Cl	X		-NHCH ₂ CH ₂ -	H	CH ₃	H


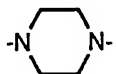

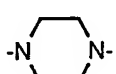
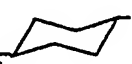
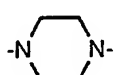
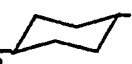
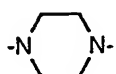
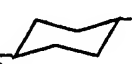
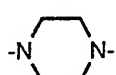

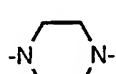
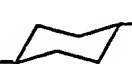
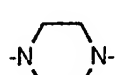
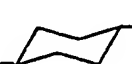
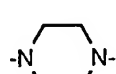
Ex.#	R ¹	R ²	A	L	B	E	P
1015	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1016	Cl	X			*	H	COCH ₃
1017	Cl	X			H	H	COCH ₂ Cl
1018	Cl	X			H	H	COC ₄ H ₉
1019	Cl	X			H	CH ₃	COCH ₃
1020	Cl	X			H	C ₂ H ₅	COCH ₃
1021	Cl	X			*	H	H
1022	Cl	X			H	CH ₃	H

SUBSTITUTE SHEET

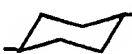
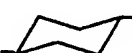
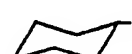
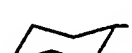
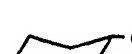



Ex.#	R ¹	R ²	A	L	B	E	P
1023	Cl	X			H	C ₂ H ₅	H
1024	Cl	X		-NH-	H	H	COCH ₃
1025	Cl	X		-NH-	H	H	COCH ₂ Cl
1026	Cl	X		-NH-	H	H	COC ₄ H ₉
1027	Cl	X		-NH-	H	CH ₃	COCH ₃
1028	Cl	X		-NH-	H	C ₂ H ₅	COCH ₃
1029	Cl	X		-NH-	H	H	H
1030	Cl	X		-NH-	H	CH ₃	H










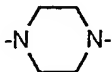
Ex.#	R ¹	R ²	A	L	B	E	P
1031	Cl	X	-CH ₂ CH ₂ - 	-NH-	H	C ₂ H ₅	H
1032	Cl	X	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	H	COCH ₃
1033	Cl	X	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1034	Cl	X	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1035	Cl	X	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1036	Cl	X	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1037	Cl	X	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	H	H
1038	Cl	X	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	CH ₃	H
1039	Cl	X	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H

SUBSTITUTE SHEET


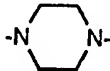



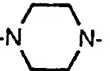

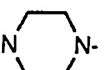

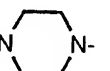

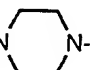

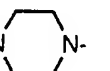

Ex.#	R ¹	R ²	A	L	B	E	P
1040	Cl	X	-CH ₂ CH ₂ - 		*	H	COCH ₃
1041	Cl	X	-CH ₂ CH ₂ - 		H	H	COCH ₂ Cl
1042	Cl	X	-CH ₂ CH ₂ - 		H	H	COC ₄ H ₉
1043	Cl	X	-CH ₂ CH ₂ - 		H	CH ₃	COCH ₃
1044	Cl	X	-CH ₂ CH ₂ - 		H	C ₂ H ₅	COCH ₃
1045	Cl	X	-CH ₂ CH ₂ - 		*	H	H
1046	Cl	X	-CH ₂ CH ₂ - 		H	CH ₃	H
1047	Cl	X	-CH ₂ CH ₂ - 		H	C ₂ H ₅	H

SUBSTITUTE SHEET

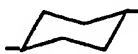
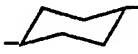
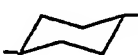
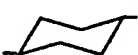
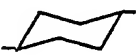
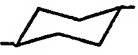
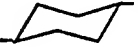
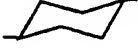

Ex.#	R ¹	R ²	A	L	B	E	P
1048	Cl	X	 CH ₂ -	-NH-	H	H	COCH ₃
1049	Cl	X	 CH ₂ -	-NH-	H	H	COCH ₂ Cl
1050	Cl	X	 CH ₂ -	-NH-	H	H	COC ₄ H ₉
1051	Cl	X	 CH ₂ -	-NH-	H	CH ₃	COCH ₃
1052	Cl	X	 CH ₂ -	-NH-	H	C ₂ H ₅	COCH ₃
1053	Cl	X	 CH ₂ -	-NH-	H	H	H
1054	Cl	X	 CH ₂ -	-NH-	H	CH ₃	H
1055	Cl	X	 CH ₂ -	-NH-	H	C ₂ H ₅	H

Ex.#	R ¹	R ²	A	L	B	E	P
1056	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₃
1057	Cl	X		-NH-	H	H	COCH ₂ Cl
1058	Cl	X		-NH-	H	H	COC ₄ H ₉
1059	Cl	X		-NH-	H	CH ₃	COCH ₃
1060	Cl	X		-NH-	H	C ₂ H ₅	COCH ₃
1061	Cl	X		-NHCH ₂ CH ₂ -	H	H	H
1062	Cl	X		-NHCH ₂ CH ₂ -	H	CH ₃	H
1063	Cl	X		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1064	Cl	X			*	H	COCH ₃

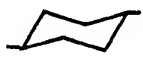
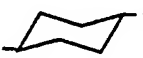





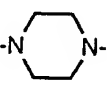

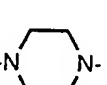
SUBSTITUTE SHEET

Ex.#	R ¹	R ²	A	L	B	E	P
1065	Cl	X			H	H	COCH ₂ Cl
1066	Cl	X			H	H	COC ₄ H ₉
1067	Cl	X			H	CH ₃	COCH ₃
1068	Cl	X			C ₂ H ₅		COCH ₃
1069	Cl	X			*	H	H
1070	Cl	X			H	CH ₃	H
1071	Cl	X			H	C ₂ H ₅	H
1072	Cl	X		-NH-	H	H	COCH ₃

SUBSTITUTE SHEET

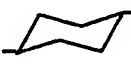
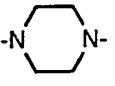
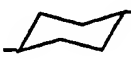
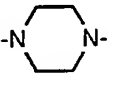
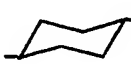
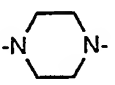
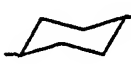
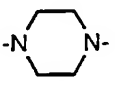
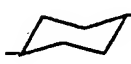
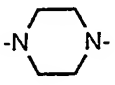
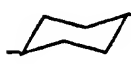
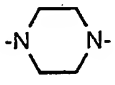


Ex.#	R ¹	R ²	A	L	B	E	P
1073	Cl	X	 CH ₂ CH ₂ -	-NH-	H	H	COCH ₂ Cl
1074	Cl	X	 CH ₂ CH ₂ -	-NH-	H	H	COC ₄ H ₉
1075	Cl	X	 CH ₂ CH ₂ -	-NH-	H	CH ₃	COCH ₃
1076	Cl	X	 CH ₂ CH ₂ -	-NH-	H	C ₂ H ₅	COCH ₃
1077	Cl	X	 CH ₂ CH ₂ -	-NH-	H	H	H
1078	Cl	X	 CH ₂ CH ₂ -	-NH-	H	CH ₃	H
1079	Cl	X	 CH ₂ CH ₂ -	-NH-	H	C ₂ H ₅	H
1080	Cl	X	 CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	H	COCH ₃
1081	Cl	X	 CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl

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Ex.#	R ¹	R ²	A	L	B	E	P
1082	Cl	X	 CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1083	Cl	X	 CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1084	Cl	X	 CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1085	Cl	X	 CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	H	H
1086	Cl	X	 CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	CH ₃	H
1087	Cl	X	 CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1088	Cl	X	 CH ₂ CH ₂ -	-N  -	×	H	COCH ₃
1089	Cl	X	 CH ₂ CH ₂ -	-N  -	H	H	COCH ₂ Cl

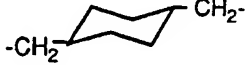
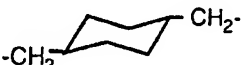



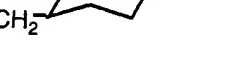


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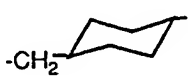
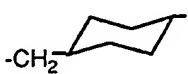
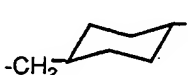
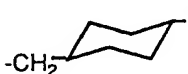
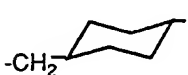
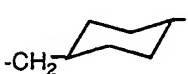
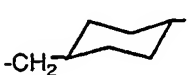
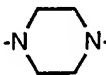
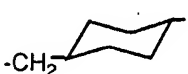
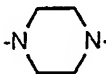
Ex.#	R ¹	R ²	A	L	B	E	P
1090	Cl	X	 CH ₂ CH ₂ -	-N  -	H	H	COC ₄ H ₉
1091	Cl	X	 CH ₂ CH ₂ -	-N  -	H	CH ₃	COCH ₃
1092	Cl	X	 CH ₂ CH ₂ -	-N  -	H	C ₂ H ₅	COCH ₃
1093	Cl	X	 CH ₂ CH ₂ -	-N  -	*	H	H
1094	Cl	X	 CH ₂ CH ₂ -	-N  -	H	CH ₃	H
1095	Cl	X	 CH ₂ CH ₂ -	-N  -	H	C ₂ H ₅	H
1096	Cl	X	-CH ₂ -  -CH ₂ -	-NH-	H	H	COCH ₃
1097	Cl	X	-CH ₂ -  -CH ₂ -	-NH-	H	H	COCH ₂ Cl

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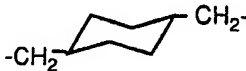


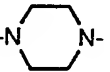

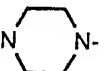

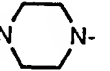

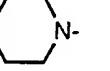

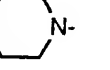
Ex.#	R ¹	R ²	A	L	B	E	P
1098	Cl	X		-NH-	H	H	COC ₄ H ₉
1099	Cl	X		-NH-	H	CH ₃	COCH ₃
1100	Cl	X		-NH-	H	C ₂ H ₅	COCH ₃
1101	Cl	X		-NH-	H	H	H
1102	Cl	X		-NH-	H	CH ₃	H
1103	Cl	X		-NH-	H	C ₂ H ₅	H
1104	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₃
1105	Cl	X		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl

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Ex.#	R ¹	R ²	A	L	B	E	P
1106	Cl	X		CH ₂ -NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1107	Cl	X		CH ₂ -NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1108	Cl	X		CH ₂ -NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1109	Cl	X		CH ₂ -NHCH ₂ CH ₂ -	H	H	H
1110	Cl	X		CH ₂ -NHCH ₂ CH ₂ -	H	CH ₃	H
1111	Cl	X		CH ₂ -NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1112	Cl	X		CH ₂ -N 	*	H	COCH ₃
1113	Cl	X		CH ₂ -N 	H	H	COCH ₂ Cl

SUBSTITUTE SHEET

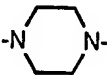
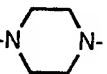
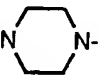
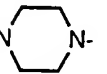
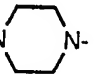
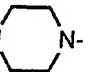
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Ex.#	R ¹	R ²	A	L	B	E	P
114	Cl	X			H	H	COC ₄ H ₉
1115	Cl	X			H	CH ₃	COCH ₃
1116	Cl	X			H	C ₂ H ₅	COCH ₃
1117	Cl	X			*	H	H
1118	Cl	X			H	CH ₃	H
1119	Cl	X			H	C ₂ H ₅	H
1120	X	Cl	single bond	-NH-	H	H	COCH ₃
1121	X	Cl	single bond	-NH-	H	H	COCH ₂ Cl
1122	X	Cl	single bond	-NH-	H	H	COC ₄ H ₉

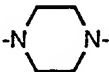
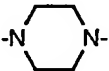
SUBSTITUTE SHEET

Ex.#	R ¹	R ²	A	L	B	E	P
1123	X	Cl	single bond	-NH-	H	CH ₃	COCH ₃
1124	X	Cl	single bond	-NH-	H	C ₂ H ₅	COCH ₃
1125	X	Cl	single bond	-NH-	H	H	H
1126	X	Cl	single bond	-NH-	H	CH ₃	H
1127	X	Cl	single bond	-NH-	H	C ₂ H ₅	H
1128	X	Cl	single bond	-NHCH ₂ CH ₂ -	H	H	COCH ₃
1129	X	Cl	single bond	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1130	X	Cl	single bond	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1131	X	Cl	single bond	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1132	X	Cl	single bond	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1133	X	Cl	single bond	-NHCH ₂ CH ₂ -	H	H	H
1134	X	Cl	single bond	-NHCH ₂ CH ₂ -	H	CH ₃	H

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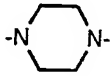
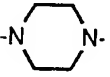

Ex.#	R ¹	R ²	A	L	B	E	P
1135	X	Cl	single bond	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1136	X	Cl	single bond		*	H	COCH ₃
1137	X	Cl	single bond		H	H	COCH ₂ Cl
1138	X	Cl	single bond		H	H	COC ₄ H ₉
1139	X	Cl	single bond		H	CH ₃	COCH ₃
1140	X	Cl	single bond		H	C ₂ H ₅	COCH ₃
1141	X	Cl	single bond		*	H	H

SUBSTITUTE SHEET

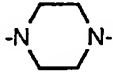

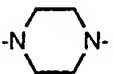
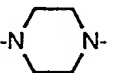
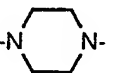
Ex.#	R ¹	R ²	A	L	B	E	P
1142	X	Cl	single bond		H	CH ₃	H
1143	X	Cl	single bond		H	C ₂ H ₅	H
1144	X	Cl	CH ₂	-NH-	H	H	COCH ₂ Cl
1145	X	Cl	CH ₂	-NH-	H	H	COC ₄ H ₉
1146	X	Cl	CH ₂	-NH-	H	CH ₃	COCH ₃
1147	X	Cl	CH ₂	-NH-	H	C ₂ H ₅	COCH ₃
1148	X	Cl	CH ₂	-NH-	H	H	H
1149	X	Cl	CH ₂	-NH-	H	CH ₃	H
1150	X	Cl	CH ₂	-NH-	H	C ₂ H ₅	H
1151	X	Cl	CH ₂	-NHCH ₂ CH ₂ -	H	H	COCH ₃
1152	X	Cl	CH ₂	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl

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Ex.#	R ¹	R ²	A	L	B	E	P
1153	X	Cl	CH ₂	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1154	X	Cl	CH ₂	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1155	X	Cl	CH ₂	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1156	X	Cl	CH ₂	-NHCH ₂ CH ₂ -	H	H	H
1157	X	Cl	CH ₂	-NHCH ₂ CH ₂ -	H	CH ₃	H
1158	X	Cl	CH ₂	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1159	X	Cl	CH ₂		*	H	COCH ₃
1160	X	Cl	CH ₂		H	H	COCH ₂ Cl
1161	X	Cl	CH ₂		H	H	COC ₄ H ₉


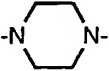

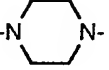
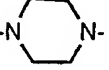
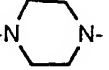
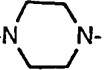
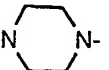
SUBSTITUTE SHEET

Ex.#	R ¹	R ²	A	L	B	E	P
1162	X	Cl	CH ₂		H	CH ₃	COCH ₃
1163	X	Cl	CH ₂		H	C ₂ H ₅	COCH ₃
1164	X	Cl	CH ₂		*	H	H
1165	X	Cl	CH ₂		H	CH ₃	H
1166	X	Cl	CH ₂		H	C ₂ H ₅	H
1167	X	Cl	CH ₂ CH ₂	-NH-	H	H	COCH ₃
1168	X	Cl	CH ₂ CH ₂	-NH-	H	H	COCH ₂ Cl
1169	X	Cl	CH ₂ CH ₂	-NH-	H	H	COC ₄ H ₉
1170	X	Cl	CH ₂ CH ₂	-NH-	H	CH ₃	COCH ₃

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Ex.#	R ¹	R ²	A	L	B	E	P
1171	X	Cl	CH ₂ CH ₂	-NH-	H	C ₂ H ₅	COCH ₃
1172	X	Cl	CH ₂ CH ₂	-NH-	H	H	H
1173	X	Cl	CH ₂ CH ₂	-NH-	H	CH ₃	H
1174	X	Cl	CH ₂ CH ₂	-NH-	H	C ₂ H ₅	H
1175	X	Cl	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	H	COCH ₃
1176	X	Cl	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1177	X	Cl	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1178	X	Cl	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1179	X	Cl	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1180	X	Cl	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	H	H
1181	X	Cl	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	CH ₃	H
1182	X	Cl	CH ₂ CH ₂	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H

SUBSTITUTE SHEET

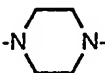
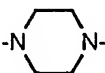
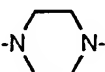
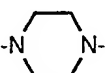
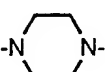
Ex.#	R ¹	R ²	A	L	B	E	P
1183	X	Cl	CH ₂ CH ₂		*	H	COCH ₃
1184	X	Cl	CH ₂ CH ₂		H	H	COCH ₂ Cl
1185	X	Cl	CH ₂ CH ₂		H	H	COC ₄ H ₉
1186	X	Cl	CH ₂ CH ₂		H	CH ₃	COCH ₃
1187	X	Cl	CH ₂ CH ₂		H	C ₂ H ₅	COCH ₃
1188	X	Cl	CH ₂ CH ₂		*	H	H
1189	X	Cl	CH ₂ CH ₂		H	CH ₃	H
1190	X	Cl	CH ₂ CH ₂		H	C ₂ H ₅	H

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Ex.#	R ¹	R ²	A	L	B	E	P
1191	X	Cl	C ₃ H ₆ (n)	-NH-	H	H	COCH ₃
1192	X	Cl	C ₃ H ₆ (n)	-NH-	H	H	COCH ₂ Cl
1193	X	Cl	C ₃ H ₆ (n)	-NH-	H	H	COC ₄ H ₉
1194	X	Cl	C ₃ H ₆ (n)	-NH-	H	CH ₃	COCH ₃
1195	X	Cl	C ₃ H ₆ (n)	-NH-	H	C ₂ H ₅	COCH ₃
1196	X	Cl	C ₃ H ₆ (n)	-NH-	H	H	H
1197	X	Cl	C ₃ H ₆ (n)	-NH-	H	CH ₃	H
1198	X	Cl	C ₃ H ₆ (n)	-NH-	H	C ₂ H ₅	H
1199	X	Cl	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H	H	COCH ₃
1200	X	Cl	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1201	X	Cl	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1202	X	Cl	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃




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Ex.#	R ¹	R ²	A	L	B	E	P
1203	X	Cl	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1204	X	Cl	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H	H	H
1205	X	Cl	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H	CH ₃	H
1206	X	Cl	C ₃ H ₆ (n)	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1207	X	Cl	C ₃ H ₆ (n)		*	H	COCH ₃
1208	X	Cl	C ₃ H ₆ (n)		H	H	COCH ₂ Cl
1209	X	Cl	C ₃ H ₆ (n)		H	H	COC ₄ H ₉
1210	X	Cl	C ₃ H ₆ (n)		H	CH ₃	COCH ₃
1211	X	Cl	C ₃ H ₆ (n)		H	C ₂ H ₅	COCH ₃

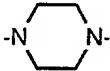

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Ex.#	R ¹	R ²	A	L	B	E	P
1212	X	Cl	C ₃ H ₆ (n)		*	H	H
1213	X	Cl	C ₃ H ₆ (n)		H	CH ₃	H
1214	X	Cl	C ₃ H ₆ (n)		H	C ₂ H ₅	H
1215	X	Cl	C ₄ H ₈ (n)	-NH-	H	H	COCH ₃
1216	X	Cl	C ₄ H ₈ (n)	-NH-	H	H	ClCH ₂ Cl
1217	X	Cl	C ₄ H ₈ (n)	-NH-	H	H	COC ₄ H ₉
1218	X	Cl	C ₄ H ₈ (n)	-NH-	H	CH ₃	COCH ₃
1219	CX	Cl	C ₄ H ₈ (n)	-NH-	H	C ₂ H ₅	COCH ₃
1220	X	Cl	C ₄ H ₈ (n)	-NH-	H	H	H
1221	X	Cl	C ₄ H ₈ (n)	-NH-	H	CH ₃	H

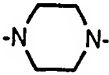
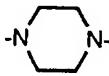
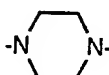
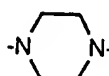
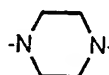
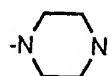
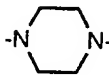

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Ex.#	R ¹	R ²	A	L	B	E	P
1222	X	Cl	C ₄ H ₈ (n)	-NH-	H	C ₂ H ₅	H
1223	X	Cl	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	H	COCH ₃
1224	X	Cl	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1225	X	Cl	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1226	X	Cl	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1227	X	Cl	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1228	X	Cl	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	H	H
1229	X	Cl	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	CH ₃	H
1230	X	Cl	C ₄ H ₈ (n)	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1231	X	Cl	C ₄ H ₈ (n)		*	H	COCH ₃
1232	X	Cl	C ₄ H ₈ (n)		H	H	COCH ₂ Cl




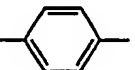
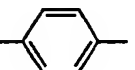
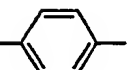
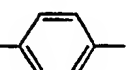
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Ex.#	R ¹	R ²	A	L	B	E	P
1233	X	Cl	C ₄ H ₈ (n)		H	H	COC ₄ H ₉
1234	X	Cl	C ₄ H ₈ (n)		H	CH ₃	COCH ₃
1235	X	Cl	C ₄ H ₈ (n)		H	C ₂ H ₅	COCH ₃
1236	X	Cl	C ₄ H ₈ (n)		*	H	H
1237	X	Cl	C ₄ H ₈ (n)		H	CH ₃	H
1238	X	Cl	C ₄ H ₈ (n)		H	C ₂ H ₅	H
1239	X	Cl		-NH-	H	H	COCH ₃
1240	X	Cl		-NH-	H	H	COCH ₂ Cl




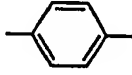
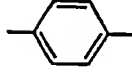
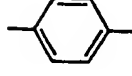
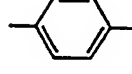
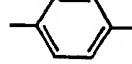

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Ex.#	R ¹	R ²	A	L	B	E	P
1241	X	Cl		-NH-	H	H	COC ₄ H ₉
1242	X	Cl		-NH-	H	CH ₃	COCH ₃
1243	X	Cl		-NH-	H	C ₂ H ₅	COCH ₃
1244	X	Cl		-NH-	H	H	H
1245	X	Cl		-NH-	H	CH ₃	H
1246	X	Cl		-NH-	H	C ₂ H ₅	H
1247	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₃






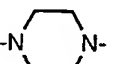
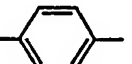
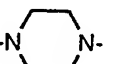
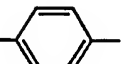
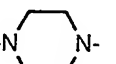
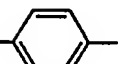
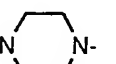
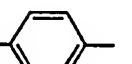
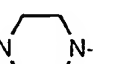
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Ex.#	R ¹	R ²	A	L	B	E	P
1248	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1249	X	Cl		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1250	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1251	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1252	X	Cl		-NHCH ₂ CH ₂ -	H	H	H
1253	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	H
1254	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1255	X	Cl			*	H	COCH ₃

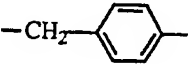
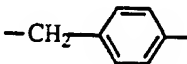
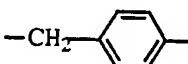
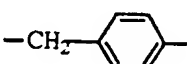
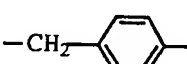
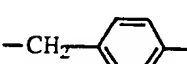
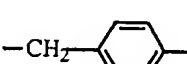
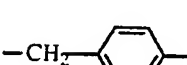
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Ex.#	R ¹	R ²	A	L	B	E	P
1256	X	Cl			H	H	COCH ₂ Cl
1257	X	Cl			H	H	COC ₄ H ₉
1258	X	Cl			H	CH ₃	COCH ₃
1259	X	Cl			H	C ₂ H ₅	COCH ₃
1260	X	Cl			*	H	H
1261	X	Cl			H	CH ₃	H
1262	X	Cl			H	C ₂ H ₅	H

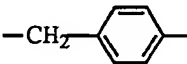
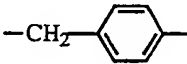
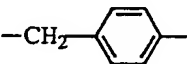
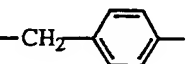
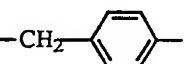
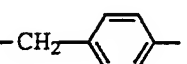
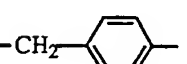
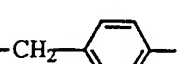
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Ex.#	R ¹	R ²	A	L	B	E	P
1263	X	Cl		-NH-	H	H	COCH ₃
1264	X	Cl		-NH-	H	H	COCH ₂ Cl
1265	X	Cl		-NH-	H	H	COC ₄ H ₉
1266	X	Cl		-NH-	H	CH ₃	COCH ₃
1267	X	Cl		-NH-	H	C ₂ H ₅	COCH ₃
1268	X	Cl		-NH-	H	H	H
1269	X	Cl		-NH-	H	CH ₃	H
1270	X	Cl		-NH-	H	C ₂ H ₅	H

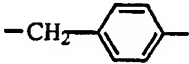
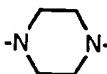
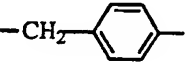
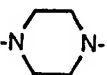
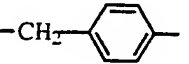
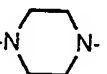
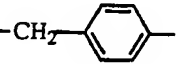
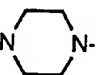
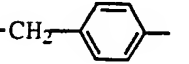
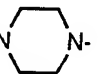
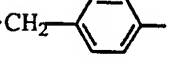
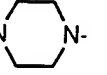
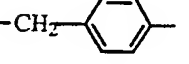
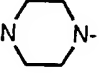

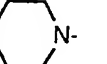
SUBSTITUTE SHEET

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Ex.#	R ¹	R ²	A	L	B	E	P
1271	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₃
1272	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1273	X	Cl		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1274	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1275	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1276	X	Cl		-NHCH ₂ CH ₂ -	H	H	H
1277	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	H
1278	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H



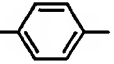





SUBSTITUTE SHEET

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Ex.#	R ¹	R ²	A	L	B	E	P
1279	X	Cl			*	H	COCH ₃
1280	X	Cl			H	H	COCH ₂ Cl
1281	X	Cl			H	H	COC ₄ H ₉
1282	X	Cl			H	CH ₃	COCH ₃
1283	X	Cl			H	C ₂ H ₅	COCH ₃
1284	X	Cl			*	H	H
1285	X	Cl			H	CH ₃	H
1286	X	Cl			H	C ₂ H ₅	H

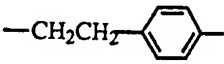
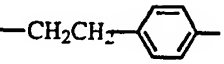
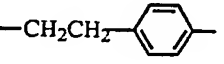
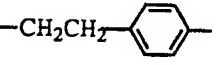
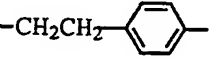
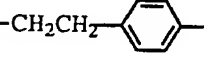
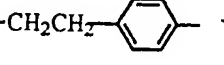
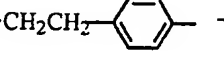
SUBSTITUTE SHEET

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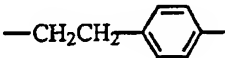

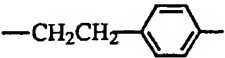

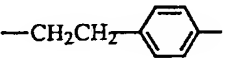

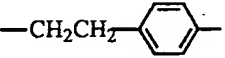

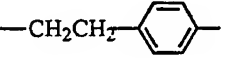

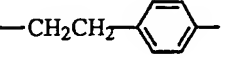
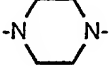
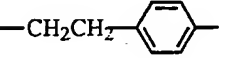
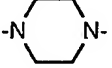
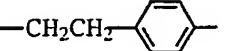

Ex.#	R ¹	R ²	A	L	B	E	P
1287	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	H	COCH_3
1288	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	H	COCH_2Cl
1289	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	H	COC_4H_9
1290	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	CH_3	COCH_3
1291	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	C_2H_5	COCH_3
1292	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	H	H
1293	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	CH_3	H
1294	X	Cl	$-\text{CH}_2\text{CH}_2-$ 	$-\text{NH}-$	H	C_2H_5	H

SUBSTITUTE SHEET

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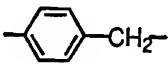
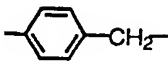
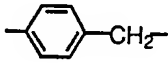
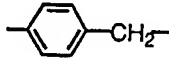
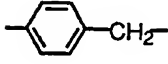
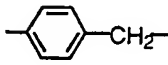
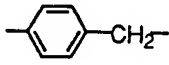
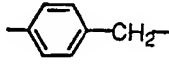
Ex.#	R ¹	R ²	A	L	B	E	P
1295	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₃
1296	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1297	X	Cl		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1298	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1299	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1300	X	Cl		-NHCH ₂ CH ₂ -	H	H	H
1301	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	H
1302	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H

SUBSTITUTE SHEET

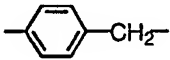
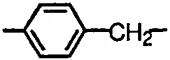
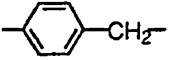
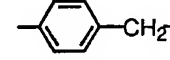
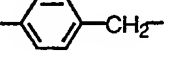
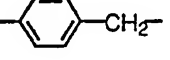
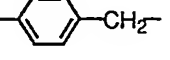
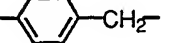
Ex.#	R ¹	R ²	A	L	B	E	P
1303	X	Cl		 *	H	H	COCH ₃
1304	X	Cl		 H	H	H	COCH ₂ Cl
1305	X	Cl		 H	H	H	COC ₄ H ₉
1306	X	Cl		 H	H	CH ₃	COCH ₃
1307	X	Cl		 H	H	C ₂ H ₅	COCH ₃
1308	X	Cl		 *	H	H	H
1309	X	Cl		 H	H	CH ₃	H
1310	X	Cl		 H	H	C ₂ H ₅	H

SUBSTITUTE SHEET

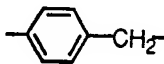
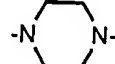
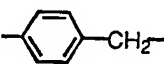

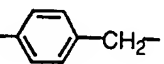
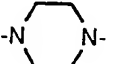
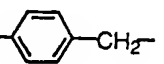
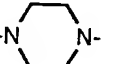
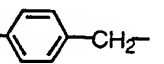
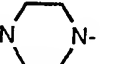
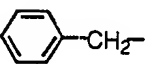
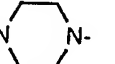
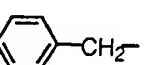
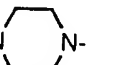
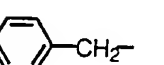
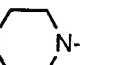
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Ex.#	R ¹	R ²	A	L	B	E	P
1311 X	Cl		-NH-	H	H	COCH ₃	
1312 X	Cl		-NH-	H	H	COCH ₂ Cl	
1313 X	Cl		-NH-	H	H	COC ₄ H ₉	
1314 X	Cl		-NH-	H	CH ₃	COCH ₃	
1315 X	Cl		-NH-	H	C ₂ H ₅	COCH ₃	
1316 X	Cl		-NH-	H	H	H	
1317 X	Cl		-NH-	H	CH ₃	H	
1318 X	Cl		-NH-	H	C ₂ H ₅	H	

SUBSTITUTE SHEET









Ex.#	R ¹	R ²	A	L	B	E	P
1319	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₃
1320	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1321	X	Cl		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1322	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1323	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1324	X	Cl		-NHCH ₂ CH ₂ -	H	H	H
1325	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	H
1326	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H

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Ex.#	R ¹	R ²	A	L	B	E	P
1327	X	Cl			*	H	COCH ₃
1328	X	Cl			H	H	COCH ₂ Cl
1329	X	Cl			H	H	COC ₄ H ₉
1330	X	Cl			H	CH ₃	COCH ₃
1331	X	Cl			H	C ₂ H ₅	COCH ₃
1332	X	Cl			*	H	H
1333	X	Cl			H	CH ₃	H
1334	X	Cl			H	C ₂ H ₅	H









SUBSTITUTE SHEET

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
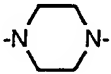

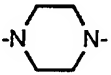

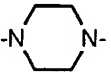

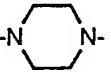

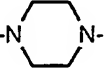

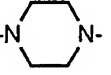

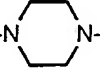

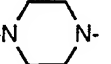
Ex.#	R ¹	R ²	A	L	B	E	P
1335	X	Cl	 -CH ₂ -CH ₂ -	-NH-	H	H	COCH ₃
1336	X	Cl	 -CH ₂ -CH ₂ -	-NH-	H	H	COCH ₂ Cl
1337	X	Cl	 -CH ₂ -CH ₂ -	-NH-	H	H	COC ₄ H ₉
1338	X	Cl	 -CH ₂ -CH ₂ -	-NH-	H	CH ₃	COCH ₃
1339	X	Cl	 -CH ₂ -CH ₂ -	-NH-	H	C ₂ H ₅	COCH ₃
1340	X	Cl	 -CH ₂ -CH ₂ -	-NH-	H	H	H
1341	X	Cl	 -CH ₂ -CH ₂ -	-NH-	H	CH ₃	H
1342	X	Cl	 -CH ₂ -CH ₂ -	-NH-	H	C ₂ H ₅	H

SUBSTITUTE SHEET









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Ex.#	R ¹	R ²	A	L	B	E	P
1343	X	Cl	 -CH ₂ -CH ₂ -NHCH ₂ CH ₂ -	H	H		COCH ₃
1344	X	Cl	 -CH ₂ -CH ₂ -NHCH ₂ CH ₂ -	H	H		COCH ₂ Cl
1345	X	Cl	 -CH ₂ -CH ₂ -NHCH ₂ CH ₂ -	H	H		COC ₄ H ₉
1346	X	Cl	 -CH ₂ -CH ₂ -NHCH ₂ CH ₂ -	H	CH ₃		COCH ₃
1347	X	Cl	 -CH ₂ -CH ₂ -NHCH ₂ CH ₂ -	H	C ₂ H ₅		COCH ₃
1348	X	Cl	 -CH ₂ -CH ₂ -NHCH ₂ CH ₂ -	H	H		H
1349	X	Cl	 -CH ₂ -CH ₂ -NHCH ₂ CH ₂ -	H	CH ₃		H
1350	X	Cl	 -CH ₂ -CH ₂ -NHCH ₂ CH ₂ -	H	C ₂ H ₅		H

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Ex.#	R ¹	R ²	A	L	B	E	P
1351	X	Cl	 -CH ₂ -CH ₂ -		*	H	COCH ₃
1352	X	Cl	 -CH ₂ -CH ₂ -		H	H	COCH ₂ Cl
1353	X	Cl	 -CH ₂ -CH ₂ -		H	H	COC ₄ H ₉
1354	X	Cl	 -CH ₂ -CH ₂ -		H	CH ₃	COCH ₃
1355	X	Cl	 -CH ₂ -CH ₂ -		H	C ₂ H ₅	COCH ₃
1356	X	Cl	 -CH ₂ -CH ₂ -		*	H	H
1357	X	Cl	 -CH ₂ -CH ₂ -		H	CH ₃	H
1358	X	Cl	 -CH ₂ -CH ₂ -		H	C ₂ H ₅	H

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Ex.#	R ¹	R ²	A	L	B	E	P
1359 X	Cl			-NH-	H	H	COCH ₃
1360 X	Cl			NH-	H	H	COCH ₂ Cl
1361 X	Cl			-NH-	H	H	COC ₄ H ₉
1362 X	Cl			-NH-	H	CH ₃	COCH ₃
1363 X	Cl			-NH-	H	C ₂ H ₅	COCH ₃
1364 X	Cl			-NH-	H	H	H
1365 X	Cl			-NH-	H	CH ₃	H
1366 X	Cl			-NH-	H	C ₂ H ₅	H

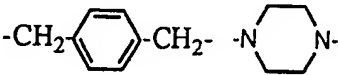
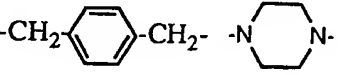
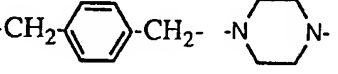
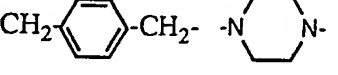
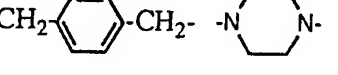
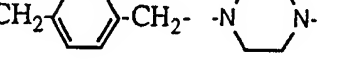
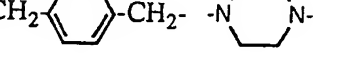
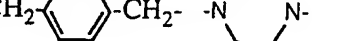
SUBSTITUTE SHEET

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Ex.#	R ¹	R ²	A	L	B	E	P
1367	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	COCH_3
1368	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	COCH_2Cl
1369	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	COC_4H_9
1370	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	CH_3	COCH_3
1371	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	C_2H_5	COCH_3
1372	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	H	H
1373	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	CH_3	H
1374	X	Cl	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{CH}_2-$	$-\text{NHCH}_2\text{CH}_2-$	H	C_2H_5	H


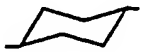
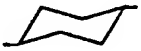
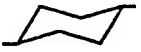

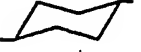



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Ex.#	R ¹	R ²	A	L	B	E	P
1375	X	Cl		*	H		COCH ₃
1376	X	Cl		H	H		COCH ₂ Cl
1377	X	Cl		H	H		COC ₄ H ₉
1378	X	Cl		H	CH ₃		COCH ₃
1379	X	Cl		H	C ₂ H ₅		COCH ₃
1380	X	Cl		*	H		H
1381	X	Cl		H	CH ₃		H
1382	X	Cl		H	C ₂ H ₅		H


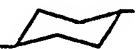
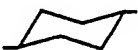
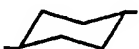
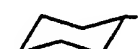

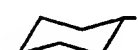
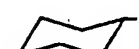
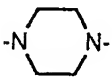

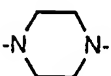
SUBSTITUTE SHEET

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Ex.#	R ¹	R ²	A	L	B	E	P
1383	X	Cl		-NH-	H	H	COCH ₃
1384	X	Cl		-NH-	H	H	COCH ₂ Cl
1385	X	Cl		-NH-	H	H	COC ₄ H ₉
1386	X	Cl		-NH-	H	CH ₃	COCH ₃
1387	X	Cl		-NH-	H	C ₂ H ₅	COCH ₃
1388	X	Cl		-NH-	H	H	H
1389	X	Cl		-NH-	H	CH ₃	H
1390	X	Cl		-NH-	H	C ₂ H ₅	H
1391	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₃



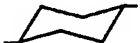

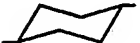

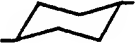

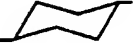

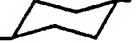
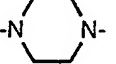


SUBSTITUTE SHEET

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Ex.#	R ¹	R ²	A	L	B	E	P
1392	X	Cl		-NHCH ₂ CH ₂ - H	F		COCH ₂ Cl
1393	X	Cl		-NHCH ₂ CH ₂ - H	H		COC ₄ H ₉
1394	X	Cl		-NHCH ₂ CH ₂ - H	CH ₃		COCH ₃
1395	X	Cl		-NHCH ₂ CH ₂ - H	C ₂ H ₅		COCH ₃
1396	X	Cl		-NHCH ₂ CH ₂ - H	H		H
1397	X	Cl		-NHCH ₂ CH ₂ - H	CH ₃		H
1398	X	Cl		-NHCH ₂ CH ₂ - H	C ₂ H ₅		H
1399	X	Cl		 *	H		COCH ₃
1400	X	Cl			H	H	COCH ₂ Cl






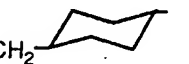
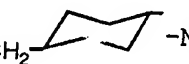

SUBSTITUTE SHEET

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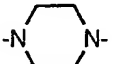

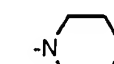
Ex.#	R ¹	R ²	A	L	B	E	P
1401	X	Cl			H	H	COC ₄ H ₉
1402	X	Cl			H	CH ₃	COCH ₃
1403	X	Cl			H	C ₂ H ₅	COCH ₃
1404	X	Cl			*	H	H
1405	X	Cl			H	CH ₃	H
1406	X	Cl			H	C ₂ H ₅	H
1407	X	Cl		-NH-	H	H	COCH ₃
1408	X	Cl		-NH-	H	H	COCH ₂ Cl

SUBSTITUTE SHEET


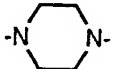
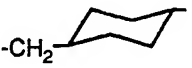


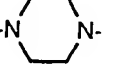

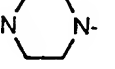
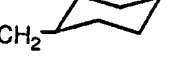
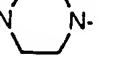

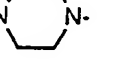
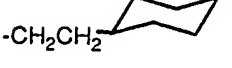

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Ex.#	R ¹	R ²	A	L	B	E	P
1409	X	Cl		-NH-	H	H	COC ₄ H ₉
1410	X	Cl		-NH-	H	CH ₃	COCH ₃
1411	X	Cl		-NH-	H	C ₂ H ₅	COCH ₃
1412	X	Cl		-NH-	H	H	H
1413	X	Cl		-NH-	H	CH ₃	H
1414	X	Cl		-NH-	H	C ₂ H ₅	H
1415	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₃
1416	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl

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Ex.#	R ¹	R ²	A	L	B	E	P
1417	X	Cl		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1418	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1419	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1420	X	Cl		-NHCH ₂ CH ₂ -	H	H	H
1421	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	H
1422	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1423	X	Cl			*	H	COCH ₃
1424	X	Cl			H	H	COCH ₂ Cl

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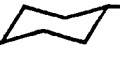

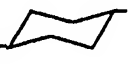
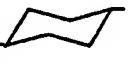
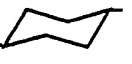


Ex.#	R ¹	R ²	A	L	B	E	P
1425	X	Cl			H	H	COC ₄ H ₉
1426	X	Cl			H	CH ₃	COCH ₃
1427	X	Cl			H	C ₂ H ₅	COCH ₃
1428	X	Cl			*	H	H
1429	X	Cl			H	CH ₃	H
1430	X	Cl			H	C ₂ H ₅	H
1431	X	Cl		-NH-	H	H	COCH ₃
1432	X	Cl		-NH-	H	H	COCH ₂ Cl

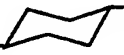
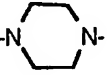
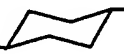
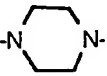
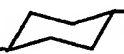
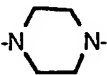
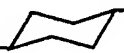
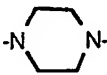
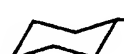
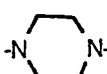
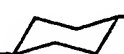
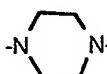
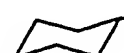
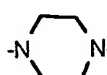
SUBSTITUTE SHEET

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Ex.#	R ¹	R ²	A	L	B	E	P
1433	X	Cl	-CH ₂ CH ₂ - 	-NH-	H	H	COC ₄ H ₉
1434	X	Cl	-CH ₂ CH ₂ - 	-NH-	H	CH ₃	COCH ₃
1435	X	Cl	-CH ₂ CH ₂ - 	-NH-	H	C ₂ H ₅	COCH ₃
1436	X	Cl	-CH ₂ CH ₂ - 	-NH-	H	H	H
1437	X	Cl	-CH ₂ CH ₂ - 	-NH-	H	CH ₃	H
1438	X	Cl	-CH ₂ CH ₂ - 	-NH-	H	C ₂ H ₅	H
1439	X	Cl	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	H	COCH ₃

SUBSTITUTE SHEET








Ex.#	R ¹	R ²	A	L	B	E	P
1440	X	Cl	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1441	X	Cl	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1442	X	Cl	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1443	X	Cl	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1444	X	Cl	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	H	H
1445	X	Cl	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	CH ₃	H
1446	X	Cl	-CH ₂ CH ₂ - 	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H

Ex.#	R ¹	R ²	A	L	B	E	P
1447	X	Cl	-CH ₂ CH ₂ - 	-N  -	*	H	COCH ₃
1448	X	Cl	-CH ₂ CH ₂ - 	-N  -	H	H	COCH ₂ Cl
1449	X	Cl	-CH ₂ CH ₂ - 	-N  -	H	H	COC ₄ H ₉
1450	X	Cl	-CH ₂ CH ₂ - 	-N  -	H	CH ₃	COCH ₃
1451	X	Cl	-CH ₂ CH ₂ - 	-N  -	H	C ₂ H ₅	COCH ₃
1452	X	Cl	-CH ₂ CH ₂ - 	-N  -	*	H	H
1453	X	Cl	-CH ₂ CH ₂ - 	-N  -	H	CH ₃	H









SUBSTITUTE SHEET

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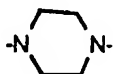



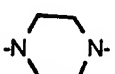

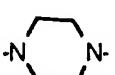

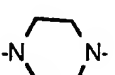
Ex.#	R ¹	R ²	A	L	B	E	P
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1454	X	Cl		H	C ₂ H ₅	H	
1455	X	Cl		H	H	COCH ₃	
1456	X	Cl		H	H	COCH ₂ Cl	
1457	X	Cl		H	H	COC ₄ H ₉	
1458	X	Cl		H	CH ₃	COCH ₃	
1459	X	Cl		H	C ₂ H ₅	COCH ₃	
1460	X	Cl		H	H	H	






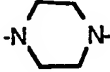



SUBSTITUTE SHEET

Ex.#	R ¹	R ²	A	L	B	E	P
1461	X	Cl		-NH-	H	CH ₃	H
1462	X	Cl		-NH-	H	C ₂ H ₅	H
1463	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₃
1464	X	Cl		-NH-	H	H	COCH ₂ Cl
1465	X	Cl		-NH-	H	H	COC ₄ H ₉
1466	X	Cl		-NH-	H	CH ₃	COCH ₃
1467	X	Cl		-NH-	H	C ₂ H ₅	COCH ₃
1468	X	Cl		-NHCH ₂ CH ₂ -	H	H	H

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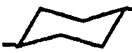
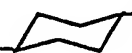
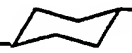
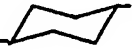
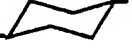
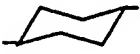
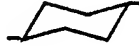
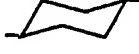

Ex.#	R ¹	R ²	A	L	B	E	P
1469	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	H
1470	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1471	X	Cl			*	H	COCH ₃
1472	X	Cl			H	H	COCH ₂ Cl
1473	X	Cl			H	H	COC ₄ H ₉
1474	X	Cl			H	CH ₃	COCH ₃
1475	X	Cl			H	C ₂ H ₅	COCH ₃

SUBSTITUTE SHEET

Ex.#	R ¹	R ²	A	L	B	E	P
1476	X	Cl			*	H	H
1477	X	Cl			H	CH ₃	H
1478	X	Cl			H	C ₂ H ₅	H
1479	X	Cl		-NH-	H	H	COCH ₃
1480	X	Cl		-NH-	H	H	COCH ₂ Cl
1481	X	Cl		-NH-	H	H	COC ₄ H ₉

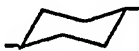
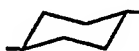
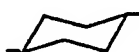

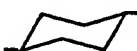
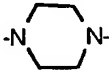

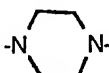

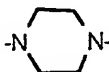

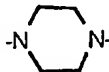

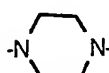
SUBSTITUTE SHEET

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Ex. #	R ¹	R ²	A	L	B	E	P
1482 X	Cl		CH ₂ CH ₂ -	-NH-	H	CH ₃	COCH ₃
1483 X	Cl		CH ₂ CH ₂ -	-NH-	H	C ₂ H ₅	COCH ₃
1484 X	Cl		CH ₂ CH ₂ -	-NH-	H	H	H
1485 X	Cl		CH ₂ CH ₂ -	-NH-	H	CH ₃	H
1486 X	Cl		CH ₂ CH ₂ -	-NH-	H	C ₂ H ₅	H
1487 X	Cl		CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	H	COCH ₃
1488 X	Cl		CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1489 X	Cl		CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1490 X	Cl		CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃

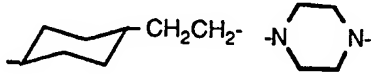
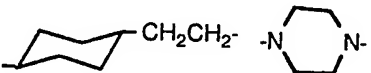
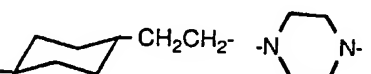
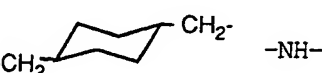
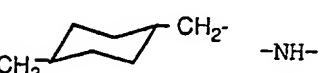
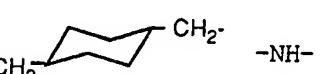
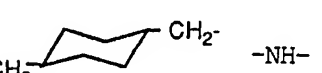
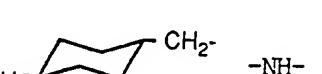
SUBSTITUTE SHEET

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Ex. #	R ¹	R ²	A	L	B	E	P
1491 X	Cl		CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃
1492 X	Cl		CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	H	H
1493 X	Cl		CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	CH ₃	H
1494 X	Cl		CH ₂ CH ₂ -	-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1495 X	Cl		CH ₂ CH ₂ -		*	H	COCH ₃
1496 X	Cl		CH ₂ CH ₂ -		H	H	COCH ₂ Cl
1497 X	Cl		CH ₂ CH ₂ -		H	H	COC ₄ H ₉
1498 X	Cl		CH ₂ CH ₂ -		H	CH ₃	COCH ₃
1499 X	Cl		CH ₂ CH ₂ -		H	C ₂ H ₅	COCH ₃


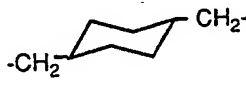

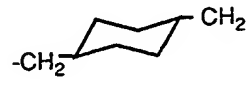
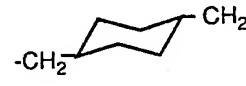
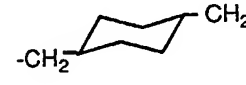
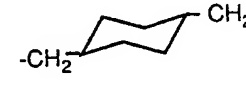
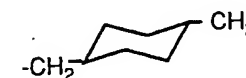
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Ex. #	R ¹	R ²	A	L	B	E	P
1500	X	Cl			*	H	H
1501	X	Cl			H	CH ₃	H
1502	X	Cl			H	C ₂ H ₅	H
1503	X	Cl			H	H	COCH ₃
1504	X	Cl			H	H	COCH ₂ Cl
1505	X	Cl			H	H	COC ₄ H ₉
1506	X	Cl			H	CH ₃	COCH ₃
1507	X	Cl			H	C ₂ H ₅	COCH ₃









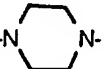

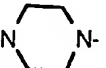

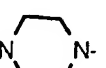
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Ex. #	R ¹	R ²	A	L	B	E	P
1508	X	Cl		-NH-	H	H	H
1509	X	Cl		-NH-	H	CH ₃	H
1510	X	Cl		-NH-	H	C ₂ H ₅	H
1511	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₃
1512	X	Cl		-NHCH ₂ CH ₂ -	H	H	COCH ₂ Cl
1513	X	Cl		-NHCH ₂ CH ₂ -	H	H	COC ₄ H ₉
1514	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	COCH ₃
1515	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	COCH ₃


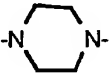

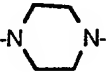
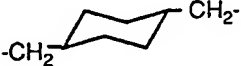
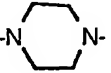
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Ex. #	R ¹	R ²	A	L	B	E	P
1516	X	Cl		-NHCH ₂ CH ₂ -	H	H	H
1517	X	Cl		-NHCH ₂ CH ₂ -	H	CH ₃	H
1518	X	Cl		-NHCH ₂ CH ₂ -	H	C ₂ H ₅	H
1519	X	Cl			*	H	COCH ₃
1520	X	Cl			H	H	COCH ₂ Cl
1521	X	Cl			H	H	COC ₄ H ₉
1522	X	Cl			H	CH ₃	COCH ₃
1523	X	Cl			H	C ₂ H ₅	COCH ₃

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Ex. #	R ¹	R ²	A	L	B	E	P
1524	X	Cl			*	H	H
1525	X	Cl			H	CH ₃	H
1526	X	Cl			H	C ₂ H ₅	H

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BIOLOGICAL EVALUATION

Compounds of Examples 1-80 are suitable angiotension II antagonists for use as the first component of conjugates of the invention. The AII receptor binding activity of many of the Example #1-#80 compounds, for example, is described in EP #253,310 published 20 January 1988. The compound of Example #5 was further evaluated in three biological assays (Assays "A", "B" and "C") for AII antagonist and blood pressure lowering properties. In two other assays, blood-pressure lowering effects of the conjugate of Example #81 were evaluated (Assays "D" and "E").

15 Assay A: Angiotensin II Binding Activity

Compound of Example #5 was tested for ability to bind to the smooth muscle angiotensin II receptor using a rat uterine membrane preparation. Angiotensin II (AII) was purchased from Peninsula Labs. ^{125}I -angiotensin II (specific activity of 2200 Ci/mmol) was purchased from Du Pont-New England Nuclear. Other chemicals were obtained from Sigma Chemical Co. This assay was carried out according to the method of Douglas et al [Endocrinology, 106, 120-124 (1980)]. Rat uterine membranes were prepared from fresh tissue. All procedures were carried out at 4°C. Uteri were stripped of fat and homogenized in phosphate-buffered saline at pH 7.4 containing 5 mM EDTA. The homogenate was centrifuged at 1500 x g for 20 min., and the supernatant was recentrifuged at 100,000 x g for 60 min. The pellet was resuspended in buffer consisting of 2 mM EDTA and 50 mM Tris-HCl (pH 7.5) to a final protein concentration of 4 mg/ml. Assay tubes were charged with 0.25 ml of a solution containing 5 mM MgCl_2 , 2 mM EDTA, 0.5% bovine serum albumin, 50 mM Tris-HCl, pH 7.5 and ^{125}I -AII (approximately 10^5 cpm) in the absence or in the presence of unlabelled ligand. The reaction was initiated by the addition of membrane protein and the mixture was

incubated at 25°C for 60 min. The incubation was terminated with ice-cold 50 mM Tris-HCl (pH 7.5) and the mixture was filtered to separate membrane-bound labelled peptide from the free ligand. The incubation tube and filter were washed with ice-cold buffer. Filters were assayed for radioactivity in a Micromedic gamma counter. Nonspecific binding was defined as binding in the presence of 10 μ M of unlabelled AII. Specific binding was calculated as total binding minus nonspecific binding. The receptor binding affinity of an AII antagonist compound was indicated by the concentration (IC₅₀) of the tested AII antagonist which gives 50% displacement of the total specifically bound ¹²⁵I-AII from the high affinity AII receptor. Binding data were analyzed by a nonlinear least-squares curve fitting program. Results are reported in Table VIII.

Assay B: In Vitro Vascular Smooth Muscle-Response for AII

Compound of Example #5 was tested for AII antagonist activity in rabbit aortic rings. Male New Zealand white rabbits (2-2.5 kg) were sacrificed using an overdose of pentobarbital and exsanguinated via the carotid arteries. The thoracic aorta was removed, cleaned of adherent fat and connective tissue and then cut into 3-mm ring segments. The endothelium was removed from the rings by gently sliding a rolled-up piece of filter paper into the vessel lumen. The rings were then mounted in a water-jacketed tissue bath, maintained at 37°C, between moveable and fixed ends of a stainless steel wire with the moveable end attached to an FT03 Grass transducer coupled to a Model 7D Grass Polygraph for recording isometric force responses. The bath was filled with 20 ml of oxygenated (95% oxygen/5% carbon dioxide) Krebs solution of the following composition (mM): 130 NaCl, 15 NaHCO₃, 15 KCl, 1.2 NaH₂PO₄, 1.2 MgSO₄, 2.5 CaCl₂, and 11.4 glucose. The preparations were equilibrated for one hour before approximately one gram of passive tension was placed on the rings. Angiotensin II concentration-response curves were then recorded (3×10^{-10}

to 1×10^{-5} M). Each concentration of AII was allowed to elicit its maximal contraction, and then AII was washed out repeatedly for 30 minutes before rechallenging with a higher concentration of AII. Aorta rings were exposed to the test antagonist at 10^{-5} M for 5 minutes before challenging with AII. Adjacent segments of the same aorta ring were used for all concentration-response curves in the presence or absence of the test antagonist. The effectiveness of the test compound was expressed in terms of pA_2 values and were calculated according to H.O. Schild [Br. J. Pharmacol. Chemother., 2,189-206 (1947)]. The pA_2 value is the concentration of the test antagonist compound which increases the EC_{50} value for AII by a factor of two. The test compound was evaluated in aorta rings from three rabbits. Results are reported in Table VIII.

TABLE VIII

In Vitro Angiotensin II
Activity of Compounds of Formula I

Test Compound	¹ Assay A	² Assay B
	IC ₅₀ (nM)	PA ₂
Ex. #5	216 ± 45	7.13 ± 0.16

15

¹Assay A: In Vitro angiotensin II Binding Activity

²Assay B: In Vitro Vascular Smooth Muscle Response

20 Assay C: In Vivo Intraduodenal and Intravenous Pressor
Assay Response for AII Antagonists

The in vivo AII receptor antagonist activity of Example #5 compound was examined in ganglion-blocked male Sprague-Dawley rats (Harlan Sprague-Dawley, Inc.), weighing 300-400 g, anesthetized with 100 mg/kg i.p. Inactin. Catheters (PE-50) were implanted in a femoral artery and vein to measure mean arterial pressure and to administer compounds, respectively. A tracheal catheter maintained airway patency. For intravenous experiments, autonomic neurotransmission was blocked by treatment with mecamylamine (3 mg/kg i.v.) and atropine (400 µg/kg i.v.). AII (30 ng/kg i.v., 20-25 µl volume) was administered four times at 10 minute intervals to establish a reproducible control pressor response. Example #5 compound was then administered at 1, 3 and 10 mg/kg in separate groups of rats as an intravenous bolus (0.2 ml volume) before rechallenging with AII

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(30 ng/kg, 20-25 μ l volume) for the following 2 hours. For intraduodenal experiments, rats were anesthetized as above, but ganglion blockade was not performed. AII was administered at 100 ng/kg i.v. (20-25 μ l volume), and
5 was administered at 10, 30 and 100 mg/kg in separate groups of rats as an intraduodenal bolus (0.2 ml volume). Angiotensin II injections were then given 5, 10, 20, 30, 45, 60, 75, 90, and 120 minutes after
10 administration of the test compound and response of arterial pressure was monitored. The response to AII was calculated as percent of the control response and then the percent inhibition was calculated as 100 minus the percent control response. Duration of action of a
15 test compound was defined as the time from peak percent inhibition to 50% of peak. The test compound was tested in two rats and the values for the two rats were averaged. Results are reported in Tables IX and X as percent of the control of AII pressor response, where "control" is defined as AII pressor response before the
20 AII antagonist test compound is administered.

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TABLE IX

In Vivo Intravenous Angiotensin II

Activity of Example #5 Compound

5 (% Control of AII Pressor Response)

	Dose (mg/kg)	Time (min)										
		1	5	10	20	30	40	50	60	75	90	120
10	1	80	85	92	90	88	86	86	89	93	95	100
	n=4	±3	±4	±4	±6	±5	±5	±6	±5	±3	±5	±0
	3	39	55	63	68	74	75	75	81	88	92	98
15	n=4	±5	±7	±8	±6	±7	±5	±3	±7	±7	±5	±1
	10	4	16	23	31	40	47	51	60	71	80	96
	n=6	±2	±2	±2	±2	±3	±4	±4	±6	±7	±8	±6

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TABLE X

In Vivo Intraduodenal Angiotensin II Activity
 of Example #5 Compound
 (% Control of AII Pressor Response)

	Dose mg/kg	Time (min)								
		1	5	10	20	30	40	50	60	75
10	10 n=3	100 ±0	94 ±4	99 ±1	85 ±11	91 ±9	91 ±9	95 ±5	93 ±7	95 ±5
	30 n=4	48 ±4	48 ±7	44 ±11	28 ±5	34 ±4	42 ±6	41 ±0	53 ±2	74 ±7
15	100 n=4	28 ±3	19 ±4	15 ±3	14 ±8	9 ±5	5 ±2	13 ±6	10 ±4	13 ±5

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Assay D: In Vivo Effects of Chronic Infusion of
Conjugate of the Invention

A conjugate of the invention as synthesized
5 in Example 81 was evaluated biologically by an in vivo
assay to determine the ability of the conjugate to
selectively inhibit renal action and thereby control
blood pressure. This in vivo experiment was conducted
to characterize the effects of the Example 81 conjugate
10 on spontaneously hypertensive rats (SHR) by acute
administration i.v. and by chronic administration i.v.
The Example 81 compound or saline vehicle was infused
continuously for four days in SHR. Mean arterial
pressure was measured (Gould Chart Recorder, model 3800;
15 Statham P23Db pressure transducer) via an indwelling
femoral artery catheter between 10:00 A. M. and 2:00 P.
M. each day. The Example 81 conjugate (10 mg/hr) or
saline was infused via a jugular vein catheter with a
Harvard infusion pump. After administration of the
20 Example 81 conjugate, there was observed a lowered mean
arterial pressure as compared to the saline vehicle
control as reported in Table XI and also in Fig. 1. A
test was conducted to determine whether the Example 81
conjugate would antagonize non-renal, vascular
25 angiotensin II receptors. In this test AII was
administered by bolus injection (100 ng/kg) to the SHR
rats (described above) on the control day and on days 1,
2 and 3 during conjugate infusion. No evidence for
systemic angiotensin II receptor antagonism was
30 observed, given the similar pressor responses to
injections of angiotensin II on the control day and days
1, 2 and 3 of infusion of the Example 81 conjugate as
shown in Table XII and also in Figure 2.

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TABLE XI

Effect of Ex. #81 Conjugate on Mean
Arterial Pressure: Chronic Administration

5

Time (days):	Control	1	2	3
MAP (mm Hg)	163	148	135	140

10

TABLE XII

15

Effect of Ex. #81 Conjugate on
AIL Pressor Response

Time (days):	Control	1	2	3
MAP (mm Hg)	44	45	65	60

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Assay "E": In Vivo Effects of Acute Infusion of Conjugate of the Invention

In this assay, a comparison was made between an
5 angiotensin II antagonist compound (Ex. #5) and a glutamyl
conjugate (Ex. #81) of the Ex. #5 AII antagonist compound
to determine the renal selectivity of the conjugate. Male
Sprague-Dawley rats (300-350 g body weight) had catheters
10 implanted into the femoral artery and vein under chloral
hydrate anesthesia (400 mg/kg, i.p.). After 2 to 4 days of
recovery, on the experimental day, a urinary bladder
catheter was implanted under methohexital anesthesia
(50 mg/kg, i.p.). Rats were placed in a restraint device
15 to allow for urine collection and mean arterial pressure
measurements. After 1-2 hours of recovery, in conscious
rats, an isotonic saline infusion (50 μ l/min) was started
and continued for the duration of the experiment. After
one hour equilibration to the saline infusion, a 20 minute
20 control urine and mean arterial pressure collection were
obtained. Then angiotensin II was infused at 20 ng/min for
25 minutes. After 5 minutes of angiotensin II infusion, a
20 minute experimental collection was made. Finally, 5
minutes after the end of angiotensin II infusion, a 20
minute recovery collection was obtained. In separate
25 groups of rats, vehicle (0.3 ml isotonic saline, i.v.
bolus), Example #5 angiotensin II antagonist compound
(100 mg/kg, i.v. bolus), or Example #81 conjugate
(100 mg/kg, i.v. bolus) was administered 1-2 minutes prior
to onset of angiotensin II infusion. Infusion of
30 angiotensin II increased mean arterial pressure and
decreased urinary sodium excretion. The Example #5 AII
antagonist compound prevented both responses to angiotensin
II. The Example #81 conjugate had no effect on the mean
arterial pressure response but prevented the
35 antinatriuretic response to angiotensin II. Angiotensin II
infusion following administration of Example #81 conjugate
actually increased urinary sodium excretion, probably due
to a pressure natriuresis. Results are shown in Tables

XIII and XIV and also in Figs. 3 and 4. Data are presented as means \pm SE. Repeated measures analysis of variance was used for main effects and interactions and Tukey's HSD test was used for pairwise comparisons among means. Statistical
5 significance was defined as $p < 0.05$.

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TABLE XIII

Effect of Ex. #81 Conjugate on
Urinary Sodium Excretion ($\mu\text{Eq}/\text{min}/100 \text{ g BW}$)

5		Control	AII	Recovery
	Vehicle	1.9 ± 0.8	$0.8 \pm 0.3^*$	1.7 ± 0.5
	Ex. #5	2.4 ± 0.5	2.5 ± 1.1	2.6 ± 0.7
10	Ex. #81	1.3 ± 0.3	$4.1 \pm 1.3^*$	1.8 ± 0.4

15

TABLE XIV

Effect of Ex. #81 Conjugate on Mean
Arterial Pressure (mm Hg): Acute Administration

20		Control	AII	Recovery
	Vehicle (n=6)	121 ± 3	$155 \pm 3^*$	123 ± 4
	Ex. #5 (n=6)	123 ± 5	125 ± 7	124 ± 7
25	Ex. #81 (n=6)	117 ± 3	$151 \pm 4^*$	121 ± 4

30

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Also embraced within this invention is a class of pharmaceutical compositions comprising one or more conjugates which comprises a first component selected from angiotensin II antagonist compounds of Formula I linked to
5 a second component provided by an enzyme-cleavable moiety. Such pharmaceutical compositions further comprise one or more non-toxic, pharmaceutically acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active
10 ingredients. The conjugates of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. Therapeutically effective doses of a conjugate of the
15 present invention required to prevent or arrest the progress of the medical condition are readily ascertained by one of ordinary skill in the art. The conjugates and composition may, for example, be administered intra-vascularly, intraperitoneally, subcutaneously, intra-
20 muscularly or topically.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical
25 composition is preferably made in the form of a dosage unit containing a particular amount of the conjugate. Examples of such dosage units are tablets or capsules. These may with advantage contain an amount of conjugate from about 1 to 250 mg, preferably from about 25 to 150 mg. A suitable
30 daily dose for a mammal may vary widely depending on the condition of the patient and other factors. However, a dose of from about 0.1 to 3000 mg/kg body weight, particularly from about 1 to 100 mg/kg body weight, may be appropriate.

The conjugate may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable carrier. A suitable daily dose is from about 0.1 to 100 mg/kg body weight injected per day in multiple doses depending on the disease being treated. A preferred daily dose would be from about 1 to 30 mg/kg body weight. Conjugates indicated for prophylactic therapy will preferably be administered in a daily dose generally in a range from about 0.1 mg to about 100 mg per kilogram of body weight per day. A more preferred dosage will be a range from about 1 mg to about 100 mg per kilogram of body weight. Most preferred is a dosage in a range from about 1 to about 50 mg per kilogram of body weight per day. A suitable dose can be administered, in multiple sub-doses per day. These sub-doses may be administered in unit dosage forms. Typically, a dose or sub-dose may contain from about 1 mg to about 100 mg of active compound per unit dosage form. A more preferred dosage will contain from about 2 mg to about 50 mg of active compound per unit dosage form. Most preferred is a dosage form containing from about 3 mg to about 25 mg of active compound per unit dose.

The dosage regimen for treating a disease condition with the conjugates and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular conjugate employed, and thus may vary widely.

For therapeutic purposes, the conjugates of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the conjugate may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium

and calcium salts of phosphoric and sulfur... acids,
gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone,
and/or polyvinyl alcohol, and then tableted or encapsulated
for convenient administration. Such capsules or tablets
5 may contain a controlled-release formulation as may be
provided in a dispersion of conjugate in
hydroxypropylmethyl cellulose. Formulations for parenteral
administration may be in the form of aqueous or non-aqueous
isotonic sterile injection solutions or suspensions. These
10 solutions and suspensions may be prepared from sterile
powders or granules having one or more of the carriers or
diluent mentioned for use in the formulations for oral
administration. The conjugates may be dissolved in water,
polyethylene glycol, propylene glycol, ethanol, corn oil,
15 cottonseed oil, peanut oil, sesame oil, benzyl alcohol,
sodium chloride, and/or various buffers. Other adjuvants
and modes of administration are well and widely known in
the pharmaceutical art.

20 Although this invention has been described with
respect to specific embodiments, the details of these
embodiments are not to be construed as limitations.
Various equivalents, changes and modifications may be made
without departing from the spirit and scope of this
25 invention, and it is understood that such equivalent
embodiments are part of this invention.

WHAT IS CLAIMED IS:

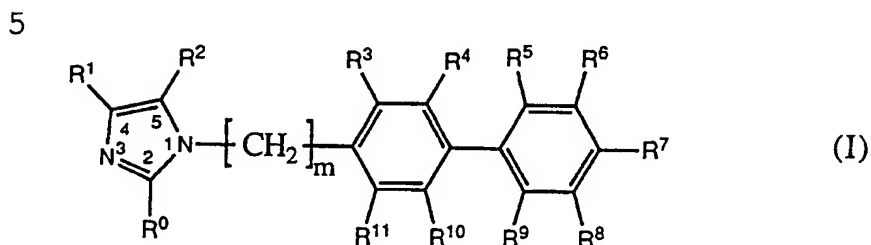
1. A conjugate comprising a residue of an
angiotensin II antagonist compound, said conjugate being
5 renal selective.

2. Conjugate of Claim 1 comprising a first
residue and a second residue, said first and second
residues connected together by a cleavable bond, wherein
10 said first residue is provided by an angiotensin II
antagonist compound, and wherein said second residue is
capable of being cleaved from said first residue
selectivity in the kidney.

3. Conjugate of Claim 2 wherein said first
and second residues are provided by precursor compounds
wherein the precursor compound of one of said first and
second residues has a reactable carboxylic acid moiety
and the precursor of the other of said first and second
20 residues has a reactable amino moiety or a moiety
convertible to a reactable amino moiety, whereby a
cleavable bond may be formed between said carboxylic
acid moiety and said amino moiety.

4. Conjugate of Claim 3 wherein said
25 angiotensin II antagonist compound providing said first
residue is selected from biphenylmethyl 1H-substituted-1,3-
imidazole compounds.

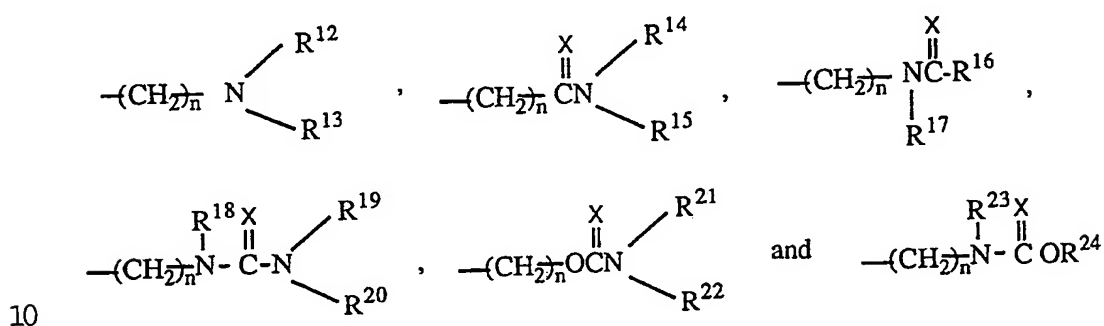
5. Conjugate of Claim 4 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:



wherein m is a number selected from one to four, inclusive;

- 10 wherein each of R⁰ through R¹¹ is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, 15 cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, 20 alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, 25 arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, 30 alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl,

arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing groups has one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{16} and R^{17} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form an aromatic heterocyclic

group having five ring members including the nitrogen atom
of said amino or amido radical and which aromatic
heterocyclic group may further contain one or more hetero
atoms as ring atoms selected from oxygen, nitrogen and
5 sulfur atoms;

and wherein each of R^3 through R^{11} may be further
independently selected from hydrido and haloalkyl, and from
acidic moieties of the formula

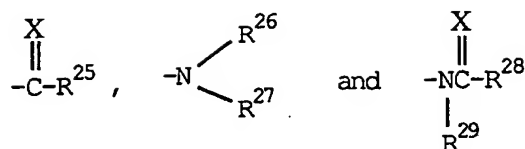
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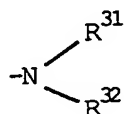
wherein n is a number selected from zero through three,
inclusive, and wherein A is an acidic group selected to
15 contain at least one acidic hydrogen atom, and the amide,
ester and salt derivatives of said acidic moieties; wherein
Y is a spacer group independently selected from one or more
of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl,
aryl, aralkyl and heteroaryl having one or more ring atoms
20 selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing R^1 through R^{24} , Y and A
groups having a substitutable position may be substituted
with one or more groups selected from hydroxy, alkyl,
25 alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl,
difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio,
alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl,
cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy,
alkoxycarbonyloxy, alkylcarbonyl, alkoxycarbonyl, carboxyl,
30 mercapto, mercaptocarbonyl, alkylthio, arylthio,
alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl,
aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl,
arylsulfonyl, heteroaryl having one or more ring atoms
selected from oxygen, sulfur and nitrogen atoms, and amino
35 and amido radicals of the formula

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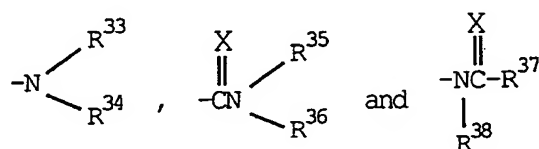


wherein X is selected from oxygen atom and sulfur atom;
 wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl,
 5 cycloalkylalkyl, aralkyl, aryl, DR³⁰ and



wherein D is selected from oxygen atom and sulfur atom and
 10 R³⁰ is selected from hydrido, alkyl, cycloalkyl,
 cycloalkylalkyl, aralkyl and aryl; wherein each of R²⁵,
 R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is independently selected
 from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl,
 haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl,
 15 alkoxycarbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl,
 arylsulfinyl, arylsulfonyl, haloalkylsulfinyl,
 haloalkylsulfonyl, aralkyl and aryl, and wherein each of
 R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is further independently
 selected from amino and amido radicals of the formula

20



wherein X is oxygen atom or sulfur atom;

25 wherein each of R³³, R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ is
 independently selected from hydrido, alkyl, cycloalkyl,
 cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl,
 cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl,
 haloalkylsulfonyl, aralkyl and aryl, and wherein R²⁶ and
 30 R²⁷ taken together and R²⁸ and R²⁹ taken together may each
 form a heterocyclic group having five to seven ring members
 including the nitrogen atom of said amino or amido radical,

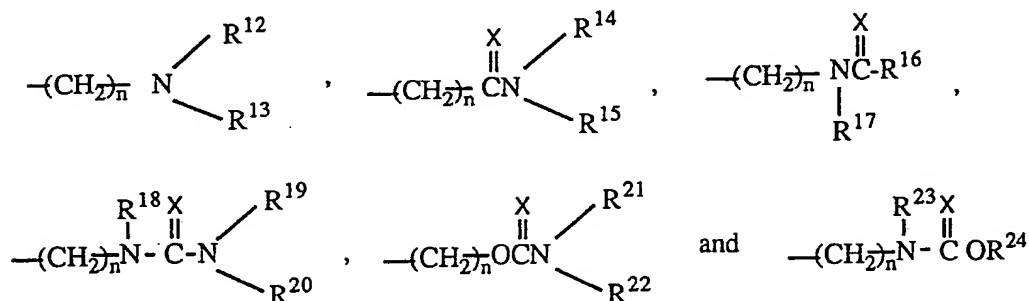
which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R²⁶ and R²⁷ taken together and R³¹ and R³² taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

with the proviso that at least one of said R¹ through R²⁴, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

6. Conjugate of Claim 5 wherein m is one; wherein each of R⁰ through R¹¹ is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio,

aralkylthiocarbonyloxy, aralkylthiocarbonylthio,
 aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto,
 alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl,
 aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido,
 5 phthalimidoalkyl, heteroaryl, heteroarylalkyl,
 cycloheteroalkyl, cycloheteroalkylalkyl and
 cycloheteroalkylcarbonylalkyl wherein each of said
 heteroaryl- and cycloheteroalkyl-containing groups has
 one or more hetero ring atoms selected from oxygen, sulfur
 10 and nitrogen atoms, and wherein each of R^0 through R^{11} may
 be further independently selected from amino and amido
 radicals of the formula



15

wherein X is selected from oxygen atom or sulfur atom;

wherein each n is a number independently selected from zero
 20 to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected
 from hydrido, alkyl, cycloalkyl, cyano, amino,
 monoalkylamino, dialkylamino, hydroxyalkyl,
 25 cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

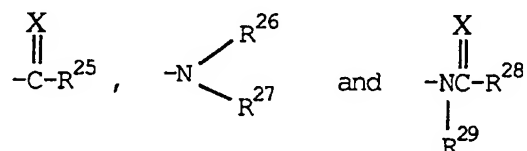
and wherein each of R^3 through R^{11} may be further
 independently selected from hydrido and haloalkyl, and from
 acidic moieties of the formula

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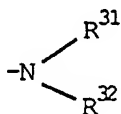


wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing R¹ through R²⁴, Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula

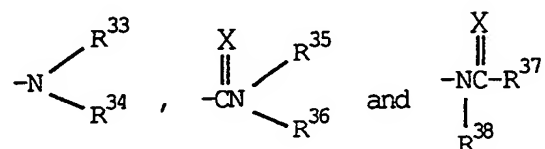


wherein X is selected from oxygen atom and sulfur atom; wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR³⁰ and



wherein D is selected from oxygen atom and sulfur atom, and R³⁰ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl.

- cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is further independently selected from amino and amido radicals of the formula

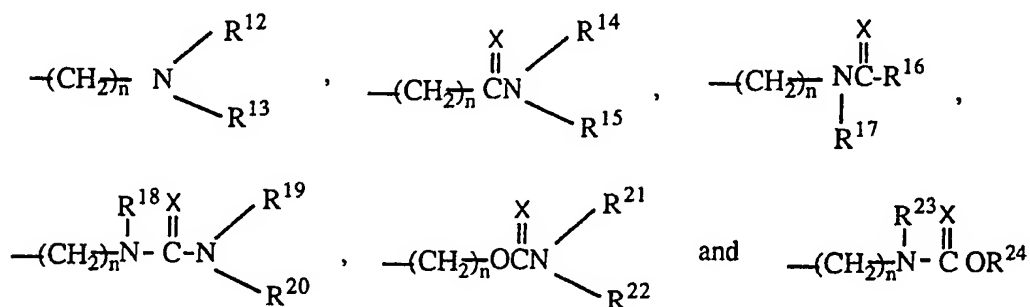


- wherein X is selected from oxygen atom or sulfur atom;
- wherein each of R²⁶ through R³¹ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;
- with the proviso that at least one of said R¹ through R²⁴, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

7. Conjugate of Claim 6 wherein m is one; wherein each of R⁰ through R¹¹ is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl,

- alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl,
 arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl,
 heteroaryl, heteroarylalkyl, cycloheteroalkyl,
 cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl
 5 wherein each of said heteroaryl- and cycloheteroalkyl-
 containing groups has one or more hetero ring atoms
 selected from oxygen, sulfur and nitrogen atoms, and
 wherein each of R^0 through R^{11} may be further independently
 selected from amino and amido radicals of the formula

10



wherein X is selected from oxygen atom or sulfur atom;

15

wherein each n is a number independently selected from zero
 to six, inclusive;

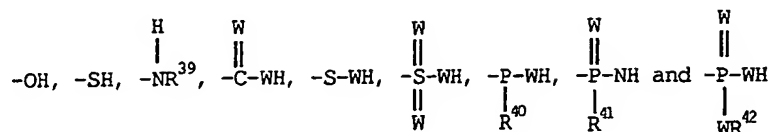
- wherein each of R^{12} through R^{24} is independently selected
 20 from hydrido, alkyl, cycloalkyl, cyano, amino,
 monoalkylamino, dialkylamino, hydroxyalkyl,
 cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

- and wherein each of R^3 through R^{11} may be an acidic moiety
 25 further independently selected from hydrido and haloalkyl,
 and from acidic moieties of the formula



- 30 wherein n is a number selected from zero through three,
 inclusive;

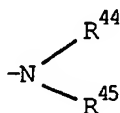
wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



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wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43} ; wherein each of R^{39} , R^{40} , R^{41} , R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl,

10 cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} , R^{40} , R^{41} and R^{42} may be further independently selected from amino radicals of the formula



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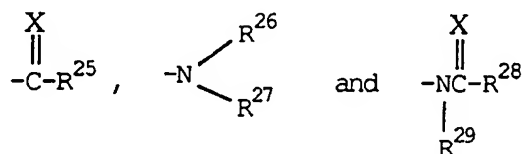
wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group

20 having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially

25 unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen

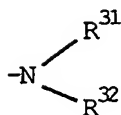
30 and sulfur atoms; wherein each of R^{40} and R^{41} may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

- wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;
- wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;
- and wherein any of the foregoing R^1 through R^{24} , Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



- wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR^{30} and

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wherein D is selected from oxygen atom and sulfur atom,
 wherein R³⁰ is selected from hydrido, alkyl, cycloalkyl,
 5 cycloalkylalkyl, aralkyl and aryl;

wherein each of R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is
 independently selected from hydrido, alkyl, cycloalkyl,
 cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl,
 10 alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl,
 haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

with the proviso that at least one of said R¹ through R²⁴,
 Y and A substituents contains a terminal primary or
 15 secondary amino moiety or a moiety convertible to a primary
 or secondary amino moiety;

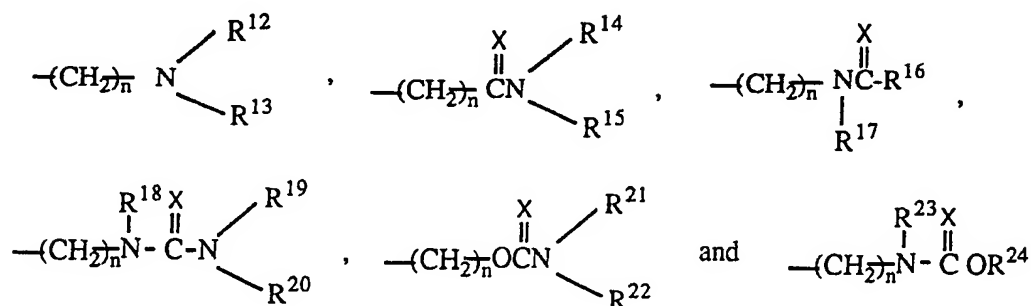
or a tautomer thereof or a pharmaceutically-acceptable salt
 thereof.

20

8. Conjugate of Claim 7 wherein m is one;
 wherein each of R⁰, R¹ and R² is independently selected
 from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl,
 cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy,
 25 aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl,
 alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl,
 cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl,
 alkylcarbonyloxy, alkylcarbonyloxyalkyl,
 alkoxycarbonylalkyl, aralkoxycarbonylalkyl,
 30 aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl,
 alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio,
 aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl,
 aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl,
 arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl,
 35 heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl

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and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R⁰ through R¹¹ may be further independently selected from amino and amido radicals of the formula



10

wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

15

wherein each of R¹² through R²⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

20

wherein each of R³ through R¹¹ is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

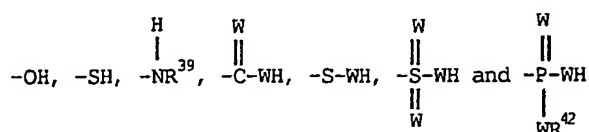
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and wherein each of R³ through R¹¹ may be an acidic moiety further independently selected from acidic moieties of the formula



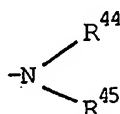
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wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



10

wherein each W is independently selected from oxygen atom, sulfur atom and NR⁴³; wherein each of R³⁹, R⁴² and R⁴³ is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R³⁹ and R⁴² may be further independently selected from amino radical of the formula



20

wherein each of R⁴⁴ and R⁴⁵ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R⁴⁴ and R⁴⁵ taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R⁴⁴ and R⁴⁵ taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen

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and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

wherein each of R^1 through R^{24} , Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxy carbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

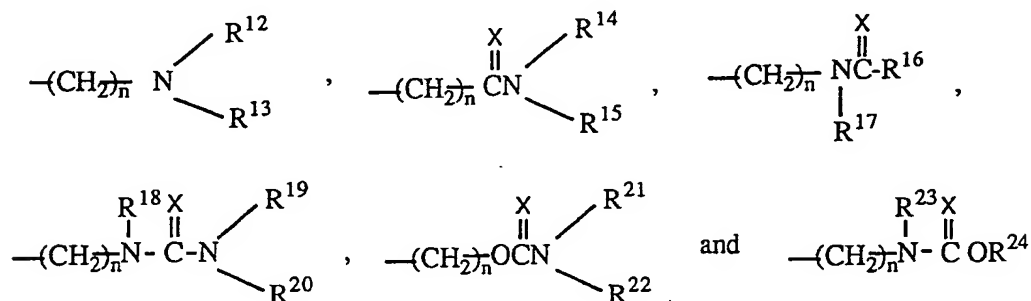
with the proviso that at least one of said R^1 through R^{24} , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

35

9. Conjugate of Claim 8 wherein m is one; wherein each of R^0 , R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl,

- cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl,
- 5 carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxy carbonylalkyl, aralkoxy carbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxy carbonyloxy, alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl,
- 10 cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be
- 15 further independently selected from amino and amido radicals of the formula



20

wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

25

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

30

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl,

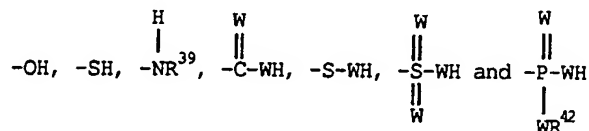
phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein each of R³ through R¹¹ may be an acidic moiety further independently selected from acidic moieties of the formula

10 -Y_nA

wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

15



wherein each W is independently selected from oxygen atom, sulfur atom and NR⁴³; wherein each of R³⁹, R⁴² and R⁴³ is
20 independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R³⁹ and R⁴² may be further independently selected from amino radical of the formula

25 

wherein each of R⁴⁴ and R⁴⁵ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from

oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be
5 attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

10

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

15

wherein each of R^1 through R^{24} , Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxy carbonyl, cyano, nitro, alkylsulfonyl,
20 haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

25

with the proviso that at least one of said R^1 through R^{24} , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

30

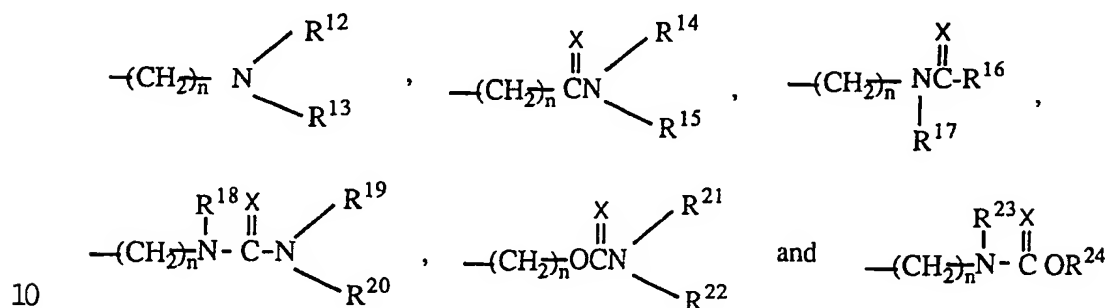
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

35

10. Conjugate of Claim 9 wherein m is one; wherein R^0 is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of R^1 and R^2 is independently selected from
alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl,

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alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano,
 nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy,
 mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy,
 alkylcarbonyloxyalkyl, alkoxycarbonylalkyl,
 5 aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl,
 phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole,
 tetrazolealkyl, alkylthio, cycloalkylthio, and amino and
 amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero
 15 to six, inclusive;

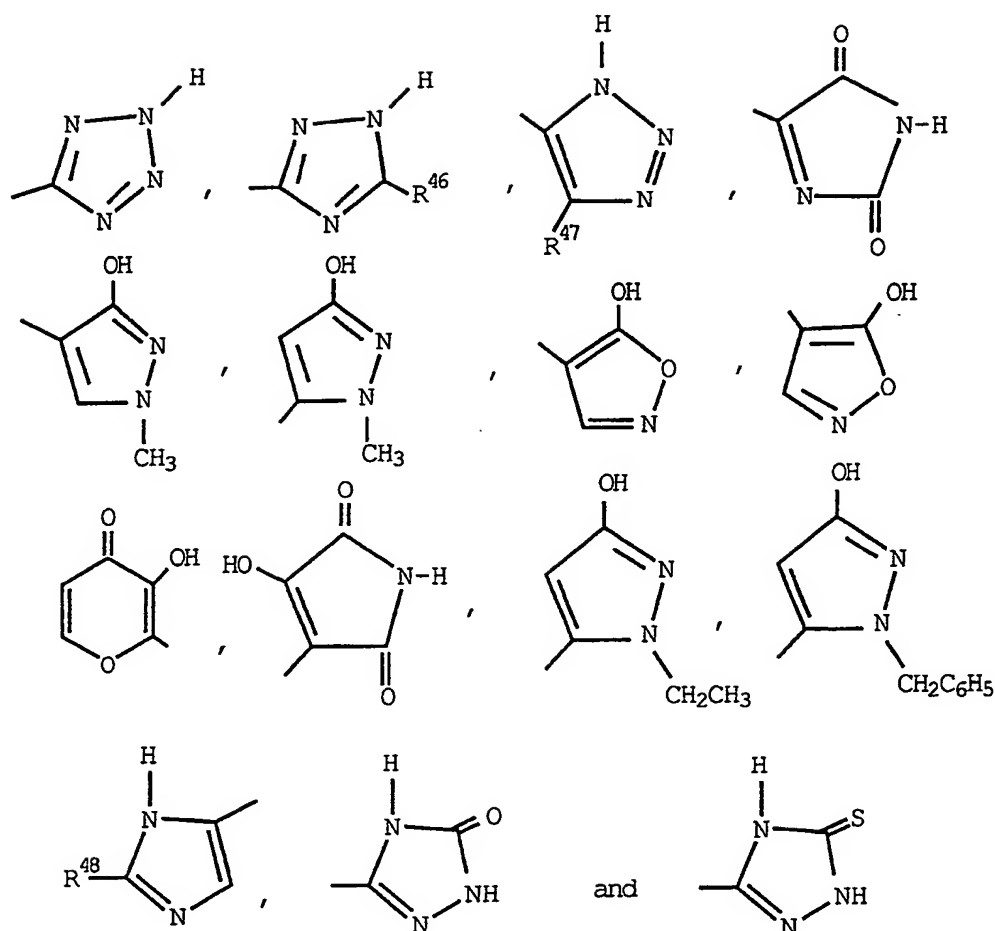
wherein each of R¹² through R²⁴ is independently selected
 from hydrido, alkyl, cycloalkyl, cyano, amino,
 hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

20 wherein each of R³ through R¹¹ is independently selected
 from hydrido, hydroxy, alkyl, hydroxyalkyl, halo,
 haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl,
 phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl,
 25 acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl,
 alkylthio and mercapto;

and wherein each of R³ through R¹¹ may be an acidic moiety
 further independently selected from acidic moieties
 30 consisting of CO₂H, CO₂CH₃, SH, CH₂SH, C₂H₄SH, PO₃H₂,
 NHSO₂CF₃, NHSO₂C₆F₅, SO₃H, CONHNH₂, CONHNHSO₂CF₃, CONHOCH₃,
 CONHOC₂H₅, CONHCF₃, OH, CH₂OH, C₂H₄OH, OPO₃H₂, OSO₃H ,

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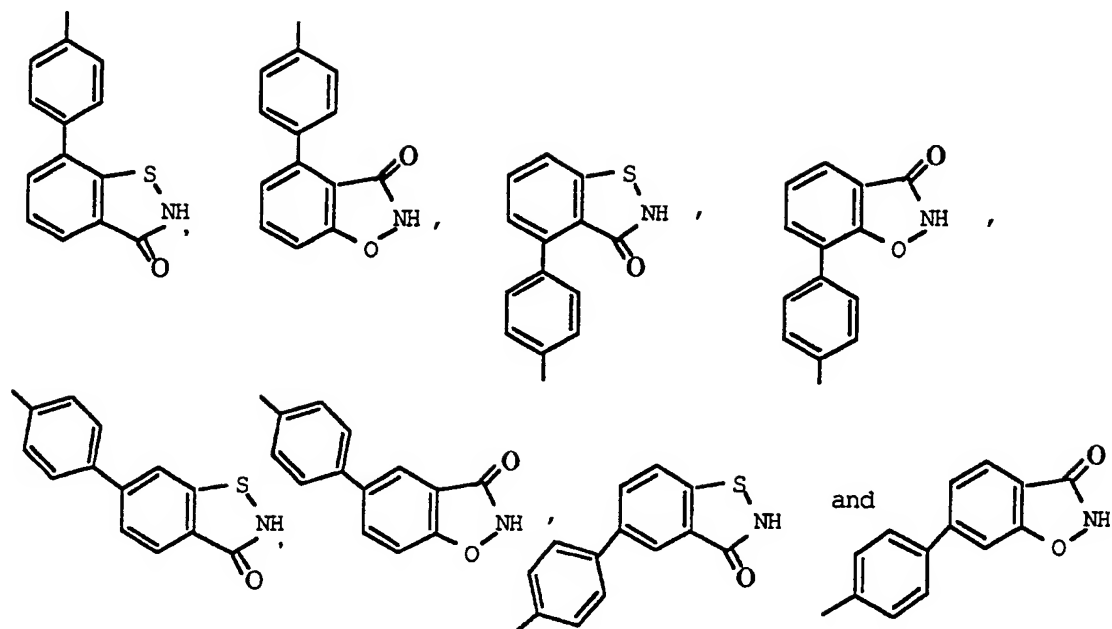
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- 5 wherein each of R⁴⁶, R⁴⁷ and R⁴⁸ is independently selected from H, Cl, CN, NO₂, CF₃, C₂F₅, C₃F₇, CHF₂, CH₂F, CO₂CH₃, CO₂C₂H₅, SO₂CH₃, SO₂CF₃ and SO₂C₆F₅; wherein Z is selected from O, S, NR⁴⁹ and CH₂; wherein R⁴⁹ is selected from hydrido, CH₃ and CH₂C₆H₅; and wherein said acidic moiety
- 10 may be a heterocyclic acidic group attached at any two adjacent positions of R³ through R¹¹ so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from
- 15




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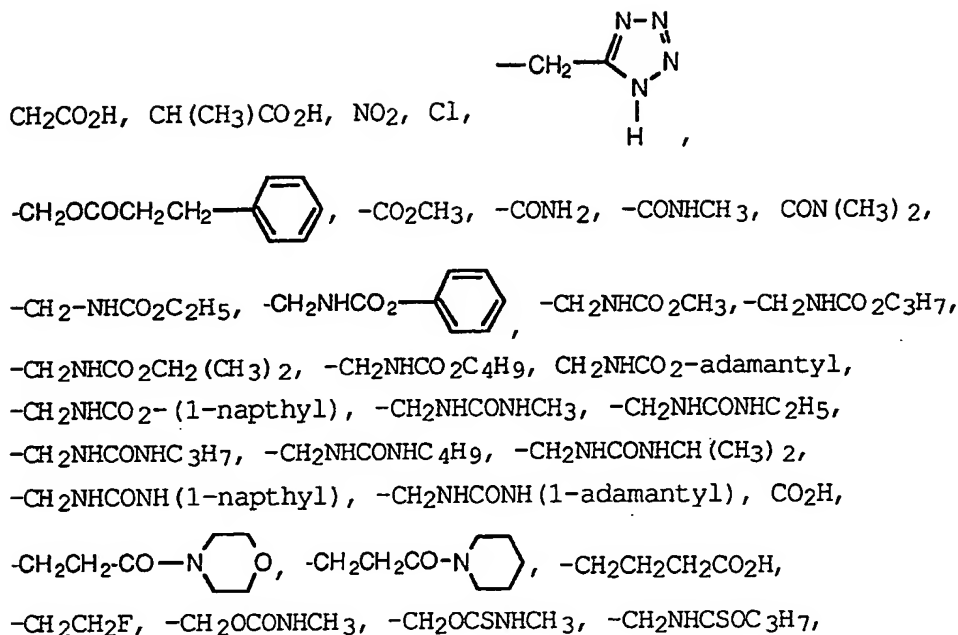


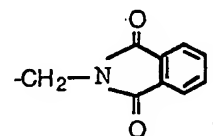

and the esters, amides and salts of said acidic moieties;

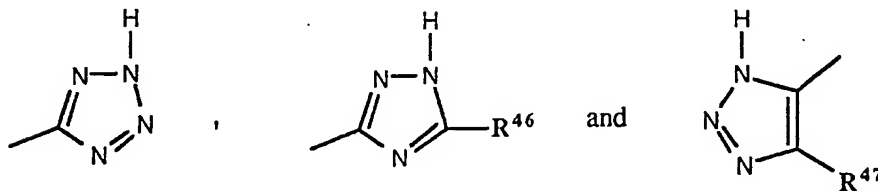
- 5 with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

11. Conjugate of Claim 10 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH=CH$, $C_3H_7(N)$, SC_3H_7 , , , C_2H_5 , $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9 ,  CH_2S , $CH_3CH=CH$ and $CH_3CH_2CH_2CH=CH-$; wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH , CH_2OCOCH_3 , CH_2Cl , Cl , CH_2OCH_3 , $CH_2OCH(CH_3)_2$, I , CHO ,

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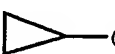



- 10 $-\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{ONO}_2$,
, $-\text{CH}_2\text{SH}$, $-\text{CH}_2\text{O}-$ ,
 12. Cl , NO_2 , CF_3 , CH_2OH , Br , F , I , methyl, ethyl, n-propyl,
 isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-
 pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl,
 cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-
 15 oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-
 dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo,
 difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-
 difluorobutyl and 1,1-difluoropentyl; wherein each of R^3
 through 11 is hydrido, with the proviso that at least one
 20 of R^5 , R^6 , R^8 and R^9 is an acidic group selected from CO_2H ,
 SH , PO_3H_2 , SO_3H , CONHNH_2 , $\text{CONHNHSO}_2\text{CF}_3$, OH ,



- 25 wherein each of R^{46} and R^{47} is independently selected from
 Cl , CN , NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

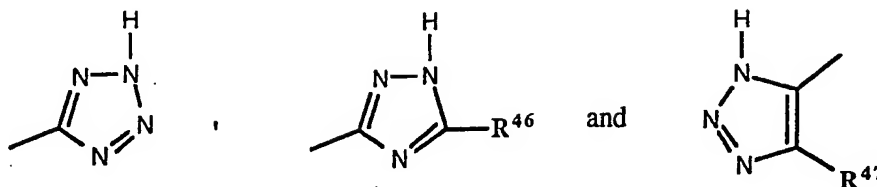
with the proviso that at least one of said R¹ through R¹¹ substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

12. Conjugate of Claim 11 wherein m is one; wherein R⁰ is selected from C₄H₉(n), CH₃CH₂CH=CH, C₃H₇(N), SC₃H₇, , , C₂H₅, C₅H₁₁(n), C₆H₁₃(n), SC₄H₉, -CH₂S, CH₃CH=CH and CH₃CH₂CH₂CH=CH-; wherein R¹ is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH₂OH, CH₂OCOCH₃, CH₂Cl, Cl, CH₂OCH₃, CH₂OCH(CH₃)₂, I, CHO, CH₂CO₂H, CH(CH₃)CO₂H, -CO₂CH₃, -CONH₂, -CONHCH₃, CON(CH₃)₂, -CH₂-NHCO₂C₂H₅, -CH₂NHCO₂-, -CH₂NHCO₂CH₃, -CH₂NHCO₂C₃H₇, -CH₂NHCO₂CH₂(CH₃)₂, -CH₂NHCO₂C₄H₉, CH₂NHCO₂-adamantyl, -CH₂NHCO₂-(1-naphthyl), -CH₂NHCONHCH₃, -CH₂NHCONHC₂H₅, -CH₂NHCONHC₃H₇, -CH₂NHCONHC₄H₉, -CH₂NHCONHCH(CH₃)₂, -CH₂NHCONH(1-naphthyl), -CH₂NHCONH(1-adamantyl), CO₂H, -CH₂CH₂-CO-N, -CH₂CH₂CH₂CO₂H, -CH₂CH₂F, -CH₂OCONHCH₃, -CH₂CH₂CH₂F, -CH₂SH and -CH₂O-;
- wherein R² is selected from H, Cl, NO₂, CF₃, CH₂OH, Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein each of R³ through R¹¹ is hydrido, with the proviso that at least one of R⁵, R⁶, R⁸ and R⁹ is an acidic group

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selected from CO_2H , SH , PO_3H_2 , SO_3H , CONHNH_2 , $\text{CONHNHSO}_2\text{CF}_3$, OH ,






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wherein each of R^{46} and R^{47} is independently selected from Cl , CN , NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

10 with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

15 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

13. Conjugate of Claim 11 wherein m is one; wherein R^0 is selected from $\text{C}_4\text{H}_9(\text{n})$, $\text{CH}_3\text{CH}_2\text{CH}=\text{CH}$, $\text{C}_3\text{H}_7(\text{N})$, SC_3H_7 , , , C_2H_5 , $\text{C}_5\text{H}_{11}(\text{n})$, $\text{C}_6\text{H}_{13}(\text{n})$,

20 SC_4H_9 , , $\text{CH}_3\text{CH}=\text{CH}$ and $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}=\text{CH}$;




wherein R^1 is selected from H , Cl , NO_2 , CF_3 , CH_2OH , Br , F , I , methyl, ethyl, n -propyl, isopropyl, n -butyl, sec -butyl, isobutyl, $tert$ -butyl, n -pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH , $\text{CH}_2\text{OCOCH}_3$, CH_2Cl , Cl , CH_2OCH_3 , $\text{CH}_2\text{OCH}(\text{CH}_3)_2$, I , CHO , $\text{CH}_2\text{CO}_2\text{H}$, $\text{CH}(\text{CH}_3)\text{CO}_2\text{H}$, $-$, $-\text{CO}_2\text{CH}_3$, $-\text{CONH}_2$, $-\text{CONHCH}_3$, $\text{CON}(\text{CH}_3)_2$,

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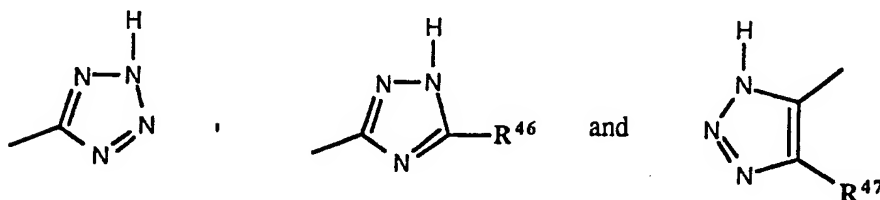
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- $-\text{CH}_2-\text{NHCO}_2\text{C}_2\text{H}_5$, $-\text{CH}_2\text{NHCO}_2-$ , $-\text{CH}_2\text{NHCO}_2\text{CH}_3$, $-\text{CH}_2\text{NHCO}_2\text{C}_3\text{H}_7$,
 $-\text{CH}_2\text{NHCO}_2\text{CH}_2(\text{CH}_3)_2$, $-\text{CH}_2\text{NHCO}_2\text{C}_4\text{H}_9$, CH_2NHCO_2 -adamantyl,
 $-\text{CH}_2\text{NHCO}_2$ -(1-naphthyl), $-\text{CH}_2\text{NHCONHCH}_3$, $-\text{CH}_2\text{NHCONHC}_2\text{H}_5$,
 $-\text{CH}_2\text{NHCONHC}_3\text{H}_7$, $-\text{CH}_2\text{NHCONHC}_4\text{H}_9$, $-\text{CH}_2\text{NHCONHCH}(\text{CH}_3)_2$,
 5 $-\text{CH}_2\text{NHCONH}(1\text{-naphthyl})$, $-\text{CH}_2\text{NHCONH}(1\text{-adamantyl})$, CO_2H ,
 $-\text{CH}_2\text{CH}_2\text{CO}-\text{N}$ , $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{OCONHCH}_3$, -
 $\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{SH}$ and $-\text{CH}_2\text{O}-$ ;

wherein each of R^3 through R^{11} is hydrido, with the proviso
 that at least one of R^5 , R^6 , R^8 and R^9 is an acidic group
 10 selected from CO_2H , SH , PO_3H_2 , SO_3H , CONHNH_2 , $\text{CONHNHSO}_2\text{CF}_3$,
 OH ,



- 15 wherein each of R^{46} and R^{47} is independently selected from
 Cl , CN , NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

with the proviso that at least one of said R^1 through R^{11}
 substituents contains a terminal primary or secondary amino
 20 moiety or a moiety convertible to a primary or secondary
 amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt
 thereof.

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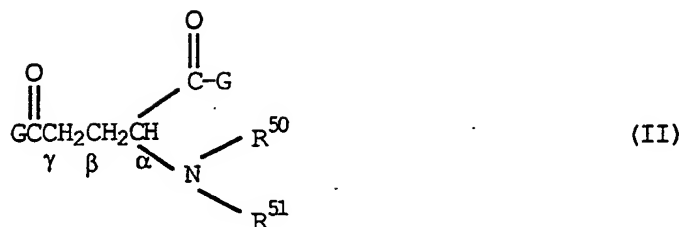
14. Conjugate of Claim 3 wherein said second
 residue forms a kidney-enzyme-cleavable amide bond with the
 residue of said angiotensin II antagonist compound.

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15. Conjugate of Claim 14 wherein said second
 residue is provided by a compound of Formula II:

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- wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxy carbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-\text{OR}^{52}$, $-\text{SR}^{53}$ and $-\text{NR}^{54}$ with each of R^{52} , R^{53} and R^{54} independently selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

16. Conjugate of Claim 15 wherein each G substituent is hydroxy.

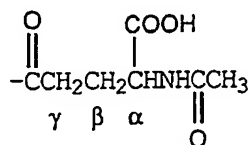
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17. Conjugate of Claim 16 wherein each G substituent is hydroxy; wherein R^{50} is hydrido; and wherein R^{51} is selected from

- 20 $-\text{CR}^{55}$ wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

18. Conjugate of Claim 17 wherein said second residue is

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19. Conjugate of Claim 18 wherein said first residue is an angiotensin II antagonist compound containing

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a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

20. Conjugate of Claim 3 wherein said first residue is an angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

21. Conjugate of Claim 20 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

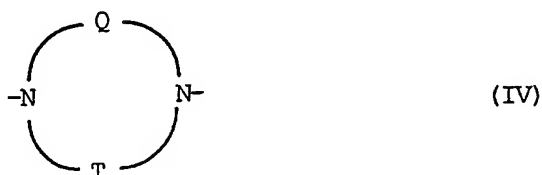
22. Conjugate of Claim 21 wherein said diamino-terminated linker group is a divalent radical of Formula III:



wherein each of R^{200} and R^{201} may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

23. Conjugate of Claim 24 wherein each of R²⁰⁰ and R²⁰¹ is hydrido.

24. Conjugate of Claim 21 wherein said diamino-terminated linker group is a divalent radical of Formula IV:



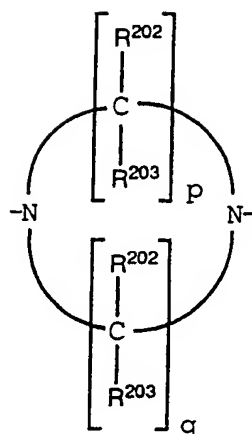
wherein each of Q and T is one or more groups independently selected from



wherein each of R²⁰² through R²⁰⁵ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, alkanoyl, alkenyl, cycloalkenyl and alkynyl.

25. Conjugate of Claim 24 wherein said diamino-terminated linker group is a divalent radical of Formula V:

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(V)

wherein each of R²⁰² and R²⁰³ is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R²⁰² and R²⁰³ is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R²⁰² or R²⁰³ is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

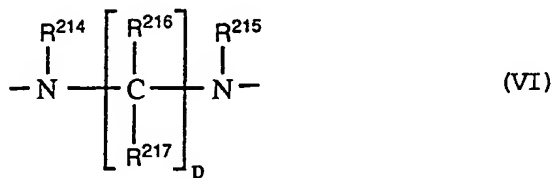
26. Conjugate of Claim 25 wherein each of R²⁰² and R²⁰³ is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

27. Conjugate of Claim 26 wherein each of R²⁰² and R²⁰³ is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

28. Conjugate of Claim 27 wherein each of R²⁰² and R²⁰³ is hydrido; and wherein each of p and q is two.

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29. Conjugate of Claim 21 wherein said diamino-terminated linker group is a divalent radical of Formula VI:



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wherein each of R²¹⁴ through R²¹⁷ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

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30. Conjugate of Claim 29 wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R²¹⁶ and R²¹⁷ is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.

20

31. Conjugate of Claim 30 wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R²¹⁶ and R²¹⁷ is independently selected from hydrido and alkyl; and wherein p is two.

25

32. Conjugate of Claim 31 wherein each of R²¹⁴, R²¹⁵, R²¹⁶ and R²¹⁷ is hydrido; and wherein p is two.

30

33. Conjugate of Claim 12 wherein said angiotensin II antagonist compound is 4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

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34. Conjugate of Claim 33 which is N-acetyl-L-glutamic acid, 5-[[4'-[2-butyl-5-chloro-4-(hydroxymethyl)-

1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

35. Conjugate of Claim 33 which is N²-acetyl-N-
5 [[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine.

36. Conjugate of Claim 33 which is N-acetyl-L-
10 glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide.

37. Conjugate of Claim 13 wherein said
15 angiotensin II antagonist compound is 4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

38. Conjugate of Claim 37 which is N-acetyl-L-
20 glutamic acid, 5-[[4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

39. Conjugate of Claim 37 which is N²-acetyl-N-
25 [[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine.

40. Conjugate of Claim 37 which is N-acetyl-L-
30 glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide.

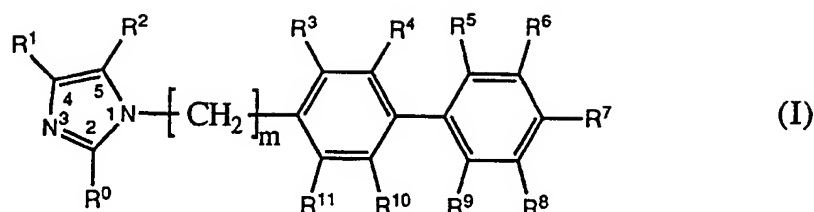
41. A pharmaceutical composition comprising one or more pharmaceutically-acceptable carriers or diluents and a therapeutically-effective amount of a renal-selective conjugate, said conjugate comprising a residue of an angiotensin II antagonist compound.

42. The composition of Claim 41 wherein said conjugate comprises first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is provided by an angiotensin II antagonist compound, and wherein said second residue is capable of being cleaved from said first residue.

43. The composition of Claim 42 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

44. The composition of Claim 43 wherein said angiotensin II antagonist compound providing said first residue is selected from biphenylmethyl 1H-substituted-1,3-imidazole compounds.

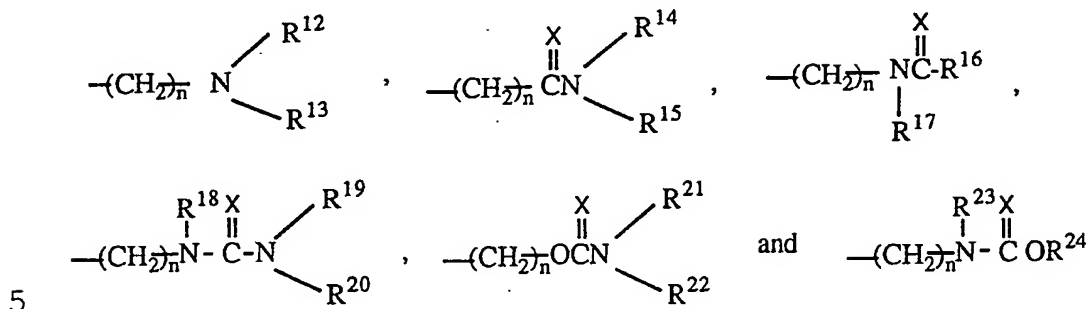
45. The composition of Claim 44 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:



wherein m is a number selected from one to four, inclusive;

- 5 wherein each of R⁰ through R¹¹ is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, 10 cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, 15 alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, 20 arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, 25 alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing 30 groups has one or more ring atoms selected from oxygen,

sulfur and nitrogen atoms, and wherein each of R⁰ through R¹¹ may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

10 wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R¹² through R²⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, 15 monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R¹² and R¹³ taken together, R¹⁴ and R¹⁵ taken together, R¹⁶ and R¹⁷ taken together, R¹⁹ and R²⁰ taken together and R²¹ and R²² taken together may each form a heterocyclic group 20 having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially 25 unsaturated; wherein R¹² and R¹³ taken together, R¹⁴ and R¹⁵ taken together, R¹⁹ and R²⁰ taken together and R²¹ and R²² taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic 30 heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

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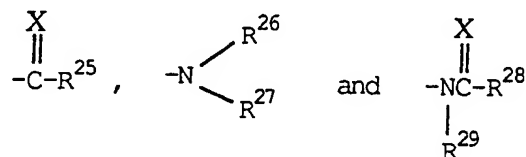
and wherein each of R³ through R¹¹ may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

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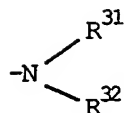
wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing R¹ through R²⁴, Y and A groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxy carbonyloxy, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



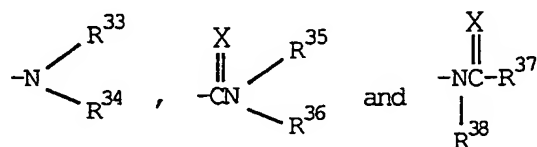
wherein X is selected from oxygen atom and sulfur atom;
35 wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR³⁰ and

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- wherein D is selected from oxygen atom and sulfur atom and
- 5 R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{25} , R^{26} , R^{27} , R^{28} , R^{29} , R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxy
- 10 carbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26} , R^{27} , R^{28} , R^{29} , R^{31} and R^{32} is further independently selected from amino and amido radicals of the formula

15



wherein X is oxygen atom or sulfur atom;

- 20 wherein each of R^{33} , R^{34} , R^{35} , R^{36} , R^{37} and R^{38} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R^{26} and
- 25 R^{27} taken together and R^{28} and R^{29} taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen
- 30 and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{26} and R^{27} taken together and R^{31} and R^{32} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical

and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

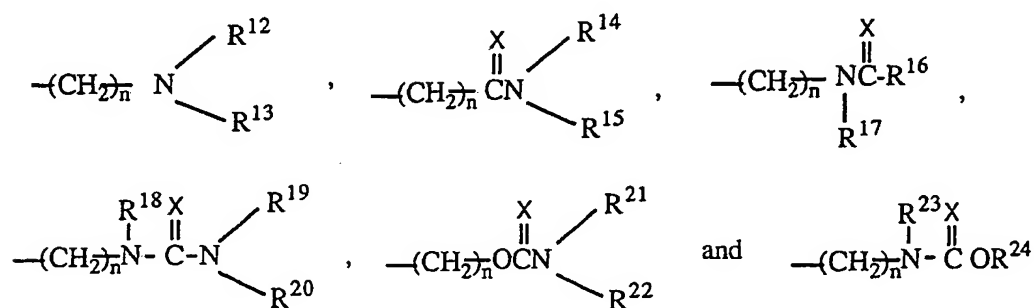
- 5 with the proviso that at least one of said R^1 through R^{24} , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

46. The composition of Claim 45 wherein m is one; wherein each of R^0 through R^{11} is independently
15 selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl,
20 carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, alkylthiocarbonyl,
25 alkylcarbonylthio, alkylthiocarbonyloxy, alkylthio-carbonylthio, alkylthiothiocarbonyl, alkylthiothio-carbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio,
30 aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido,
35 phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has

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one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula

5



wherein X is selected from oxygen atom or sulfur atom;

10

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

15

and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

20

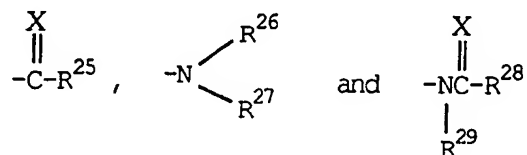


wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl,

30

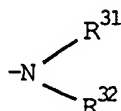
cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

- 5 and wherein any of the foregoing R^1 through R^{24} , Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the
10 formula



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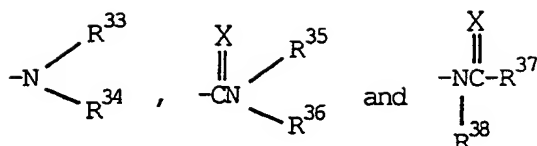
wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR^{30} and



20

- wherein D is selected from oxygen atom and sulfur atom, and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{26} , R^{27} , R^{28} , R^{29} , R^{31} and R^{32} is independently selected from
25 hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxy carbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26} , R^{27} , R^{28} , R^{29} , R^{31} and R^{32}
30 is further independently selected from amino and amido radicals of the formula

320



wherein X is selected from oxygen atom or sulfur atom;

5 wherein each of R²⁶ through R³¹ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

10

with the proviso that at least one of said R¹ through R²⁴, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

15

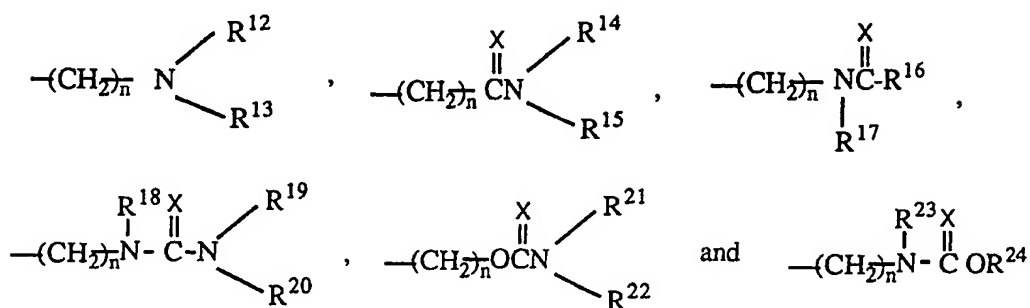
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

47. The composition of Claim 46 wherein m is
 20 one; wherein each of R⁰ through R¹¹ is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cycloalkenyl,
 25 alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxy carbonyloxy, alkylcarbonyloxyalkyl, alkoxy carbonylalkyl, aralkoxy carbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio,
 30 arylthio, aralkylthio, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and
 35 cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one

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or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula

5



wherein X is selected from oxygen atom or sulfur atom;

10

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

15

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

20



wherein n is a number selected from zero through three, inclusive;

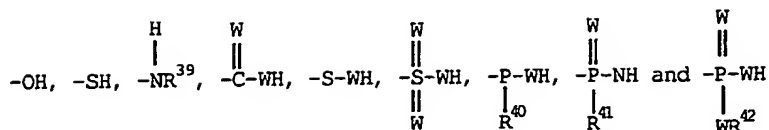
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wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

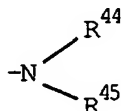
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wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43} ; wherein each of R^{39} , R^{40} , R^{41} , R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} , R^{40} , R^{41} and R^{42} may be further independently selected from amino radicals of the formula



wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R^{40} and R^{41} may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of

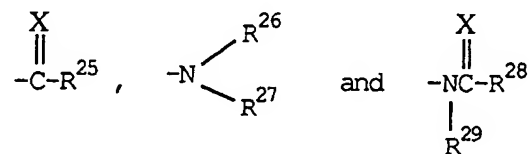
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heterocyclic rings of four to about nine ring members,
 which heterocyclic ring contains at least one hetero atom
 selected from oxygen, sulfur and nitrogen atoms, which
 heterocyclic ring may be saturated, fully unsaturated or
 5 partially unsaturated, and which heterocyclic ring may be
 attached at a single position selected from R³ through R¹¹
 or may be attached at any two adjacent positions selected
 from R³ through R¹¹ so as to form a fused-ring system with
 one of the phenyl rings of the biphenyl moiety of Formula
 10 I; and the amide, ester and salt derivatives of said
 heterocyclic acidic groups;

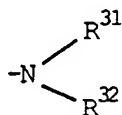
wherein Y is a spacer group independently selected from one
 or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl,
 15 aryl and aralkyl;

and wherein any of the foregoing R¹ through R²⁴, Y and A
 groups having a substitutable position may be substituted
 by one or more groups selected from alkyl, difluoroalkyl,
 20 alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy,
 aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl,
 alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio,
 alkylthiocarbonyl, and amino and amido radicals of the
 formula

25



wherein X is selected from oxygen atom and sulfur atom;
 wherein R²⁵ is selected from hydrido, alkyl, cycloalkyl,
 30 cycloalkylalkyl, aralkyl, aryl and DR³⁰ and



wherein D is selected from oxygen atom and sulfur atom,
wherein R³⁰ is selected from hydrido, alkyl, cycloalkyl,
cycloalkylalkyl, aralkyl and aryl;

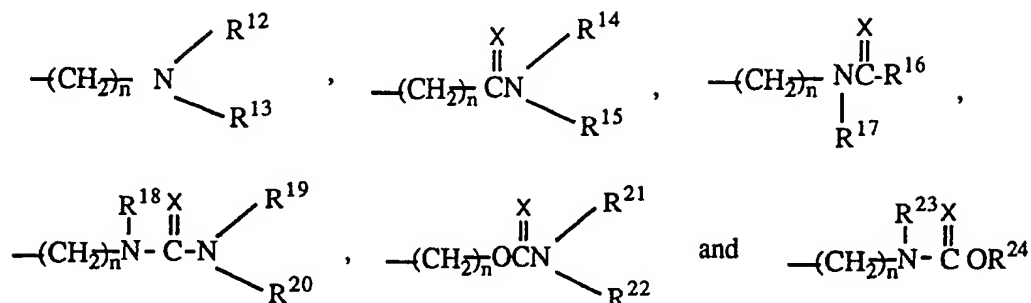
5 wherein each of R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is
independently selected from hydrido, alkyl, cycloalkyl,
cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl,
alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl,
haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

10 with the proviso that at least one of said R¹ through R²⁴,
Y and A substituents contains a terminal primary or
secondary amino moiety or a moiety convertible to a primary
or secondary amino moiety;

15 or a tautomer thereof or a pharmaceutically-acceptable salt
thereof.

48. The composition of Claim 47 wherein m is
20 one; wherein each of R⁰, R¹ and R² is independently
selected from alkyl, hydroxyalkyl, halo, haloalkyl,
cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl,
aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl,
alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkenyl,
25 alkynyl, cycloalkynyl, cyano, nitro, carboxyl,
carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl,
alkoxycarbonylalkyl, aralkoxycarbonylalkyl,
aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl,
alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio,
30 aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl,
aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl,
arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl,
heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl
and cycloheteroalkylcarbonylalkyl wherein each of said
35 heteroaryl- and cycloheteroalkyl-containing groups has one
or more hetero ring atoms selected from oxygen, sulfur and
nitrogen atoms, and wherein each of R⁰ through R¹¹ may be

further independently selected from amino and amido radicals of the formula



5

wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero
10 to six, inclusive;

wherein each of R¹² through R²⁴ is independently selected
from hydrido, alkyl, cycloalkyl, cyano, amino,
monoalkylamino, dialkylamino, hydroxyalkyl,
15 cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

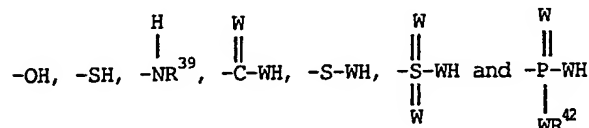
wherein each of R³ through R¹¹ is independently selected
from hydrido, hydroxy, alkyl, hydroxyalkyl, halo,
haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl,
20 aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl,
alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl,
cycloalkynyl, cyano, nitro, carboxyl, alkylthio,
aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl,
aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl,
25 arylsulfonyl and heteroaryl having one or more ring atoms
selected from oxygen, sulfur and nitrogen atoms;

and wherein each of R³ through R¹¹ may be an acidic moiety
further independently selected from acidic moieties of the
30 formula



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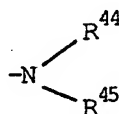
wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



5

wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43} ; wherein each of R^{39} , R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula

15



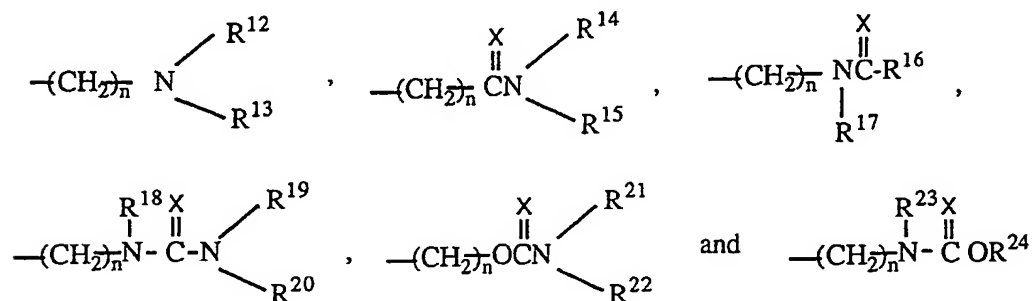
wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{44} and R^{45} taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms, and which heterocyclic group may be saturated or partially unsaturated; wherein R^{44} and R^{45} taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; and the amide, ester and salt derivatives of said acidic groups; wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one

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- hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;
- wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;
- wherein each of R^1 through R^{24} , Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxy, carbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;
- with the proviso that at least one of said R^1 through R^{24} , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- or a tautomer thereof or a pharmaceutically-acceptable salt thereof.
49. The composition of Claim 48 wherein m is one; wherein each of R^0 , R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy, carbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy,

- alkylcarbonyloxyalkyl, alkoxycarbonylalkyl,
 aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl,
 mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy,
 alkylthio, cycloalkylthio, phthalimido, phthalimidoalkyl,
 5 heteroaryl, heteroarylalkyl, cycloheteroalkyl,
 cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl
 wherein each of said heteroaryl- and cycloheteroalkyl-
 containing groups has one or more hetero ring atoms
 selected from oxygen, sulfur and nitrogen atoms, and
 10 wherein each of R^0 through R^{11} may be further independently
 selected from amino and amido radicals of the formula



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wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero
 to six, inclusive;

20

wherein each of R^{12} through R^{24} is independently selected
 from hydrido, alkyl, cycloalkyl, cyano, amino,
 hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

25

wherein each of R^3 through R^{11} is independently selected
 from hydrido, hydroxy, alkyl, hydroxyalkyl, halo,
 haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl,
 phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl,
 alkylcarbonyl, alkoxycarbonyl, alkenyl, cyano, nitro,

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carboxyl, alkylthio, mercapto and heteroaryl having one or
 more ring atoms selected from oxygen, sulfur and nitrogen
 atoms;

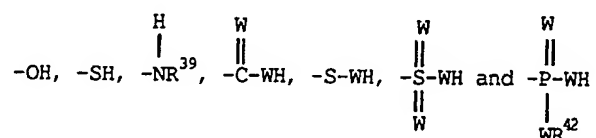
and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula

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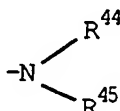
wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

10



wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43} ; wherein each of R^{39} , R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula

15



20

wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

25

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3

30

35

through R¹¹ so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

5

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

- 10 wherein each of R¹ through R²⁴, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxy carbonyl, cyano, nitro, alkylsulfonyl, 15 haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

- with the proviso that at least one of said R¹ through R²⁴, Y and A substituents contains a terminal primary or 20 secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

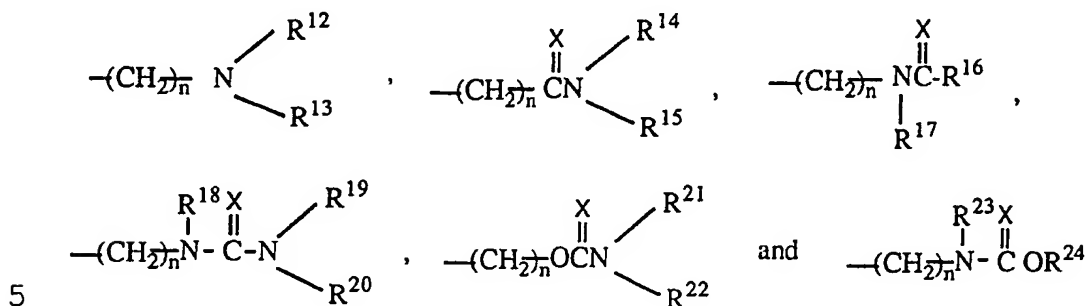
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

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50. The composition of Claim 49 wherein m is one; wherein R⁰ is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of R¹ and R² is independently selected from 30 alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, 35 nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptoalkyl, mercaptocarbonyl, alkoxy carbonyloxy, alkylcarbonyloxyalkyl, alkoxy carbonylalkyl, aralkoxy carbonylalkyl, aralkylcarbonyloxyalkyl,

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phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole, tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

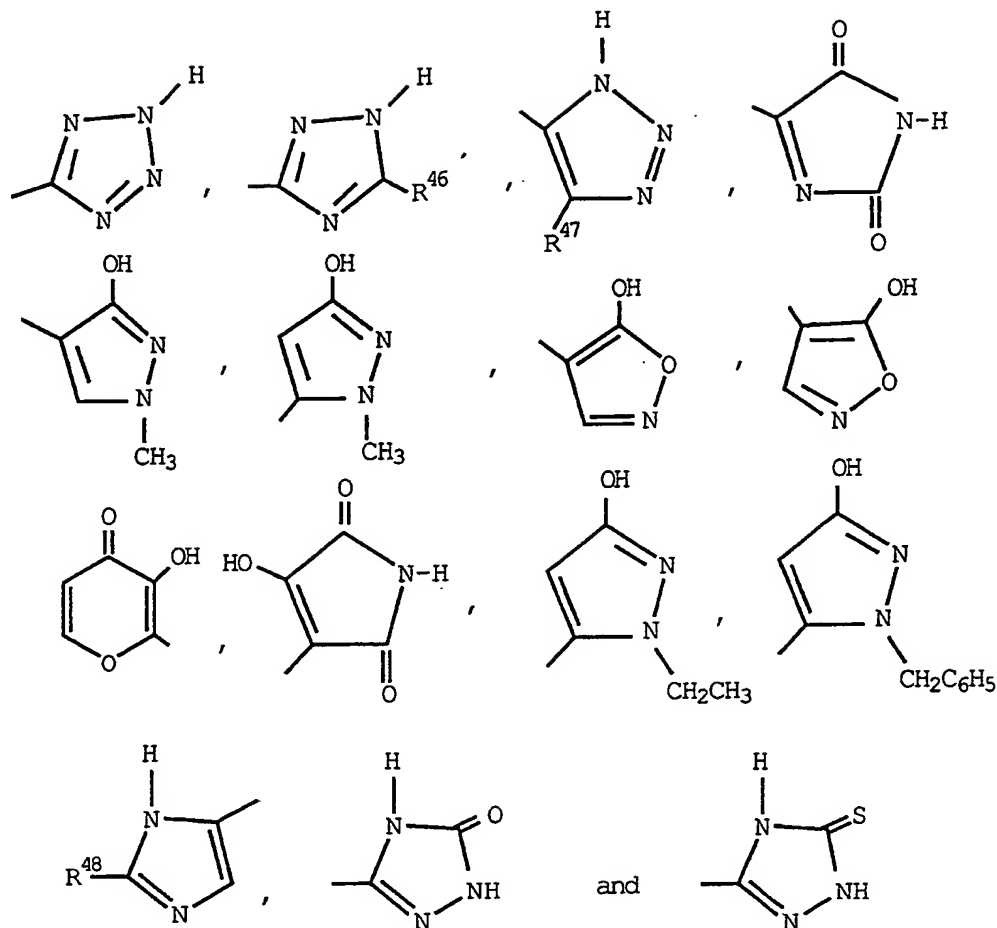
wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R¹² through R²⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R³ through R¹¹ is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxy carbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio and mercapto;

and wherein each of R³ through R¹¹ may be an acidic moiety further independently selected from acidic moieties consisting of CO₂H, CO₂CH₃, SH, CH₂SH, C₂H₄SH, PO₃H₂, NHSO₂CF₃, NHSO₂C₆F₅, SO₃H, CONHNH₂, CONHNHSO₂CF₃, CONHOCH₃, CONHOC₂H₅, CONHCF₃, OH, CH₂OH, C₂H₄OH, OPO₃H₂, OSO₃H,

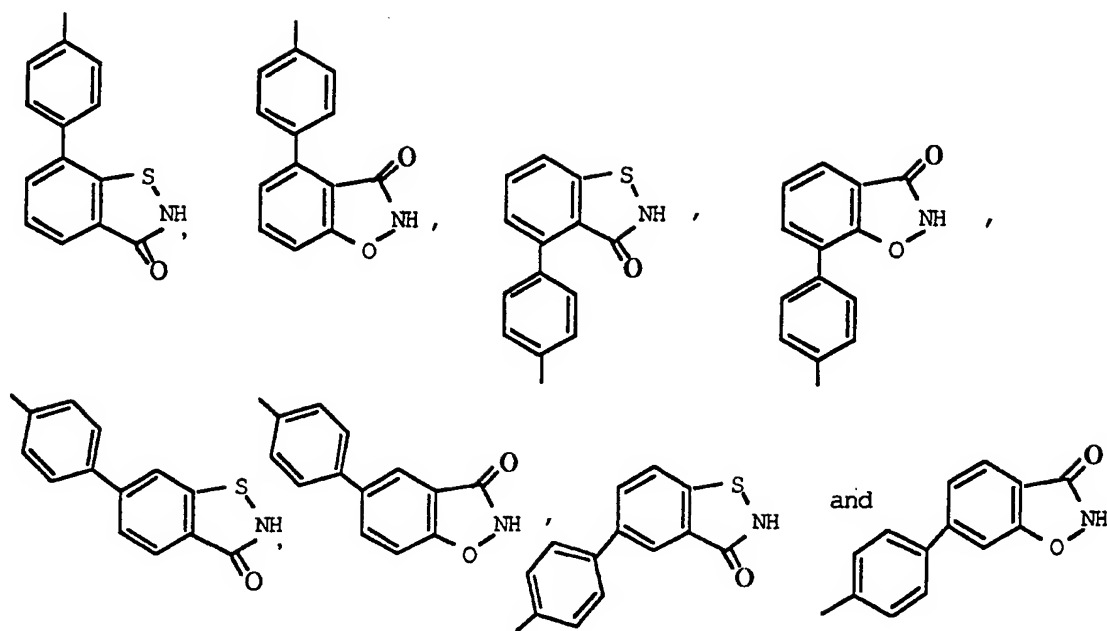
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- wherein each of R⁴⁶, R⁴⁷ and R⁴⁸ is independently selected from H, Cl, CN, NO₂, CF₃, C₂F₅, C₃F₇, CHF₂, CH₂F, CO₂CH₃, CO₂C₂H₅, SO₂CH₃, SO₂CF₃ and SO₂C₆F₅; wherein Z is selected from O, S, NR⁴⁹ and CH₂; wherein R⁴⁹ is selected from hydrido, CH₃ and CH₂C₆H₅; and wherein said acidic moiety may be a heterocyclic acidic group attached at any two adjacent positions of R³ through R¹¹ so as to form a fused ring system so as to include one of the phenyl rings of the biphenyl moiety of Formula I, said biphenyl fused ring system selected from

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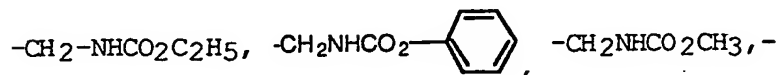
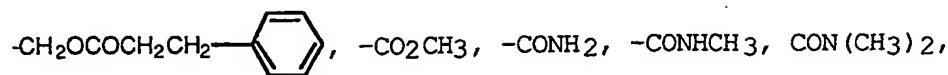
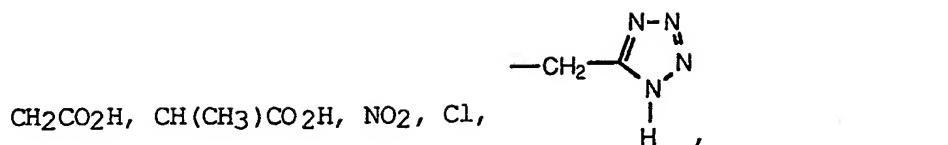
and the esters, amides and salts of said acidic moieties;

- 5 with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

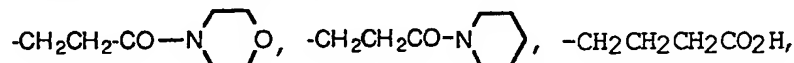
51. The composition of Claim 50 wherein m is one; wherein R^0 is selected from C_4H_9 (n), $CH_3CH_2CH=CH$,

- 15 C_3H_7 (N), SC_3H_7 ,  CH_2 , , C_2H_5 , C_5H_{11} (n), C_6H_{13} (n), SC_4H_9 ,  CH_2S , $CH_3CH=CH$ and $CH_3CH_2CH_2CH=CH$;
- wherein each of R^1 and R^2 is independently selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH , CH_2OCOCH_3 , CH_2Cl , Cl , CH_2OCH_3 , $CH_2OCH(CH_3)_2$, I , CHO ,

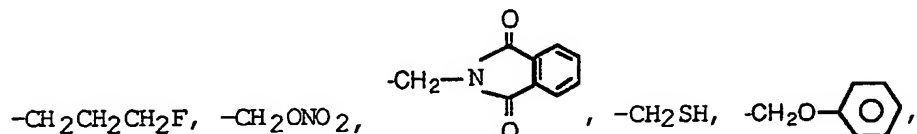
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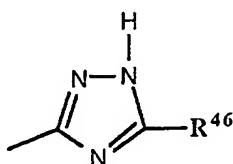
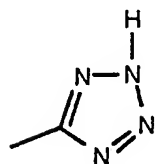
- 5 -CH₂NHCO₂CH₂(CH₃)₂, -CH₂NHCO₂C₄H₉, CH₂NHCO₂-adamantyl,
 -CH₂NHCO₂-(1-naphthyl), -CH₂NHCONHCH₃, -CH₂NHCONHC₂H₅,
 -CH₂NHCONHC₃H₇, -CH₂NHCONHC₄H₉, -CH₂NHCONHCH(CH₃)₂,
 -CH₂NHCONH(1-naphthyl), -CH₂NHCONH(1-adamantyl), CO₂H,



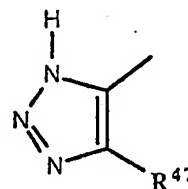
- 10 -CH₂CH₂F, -CH₂OCONHCH₃, -CH₂OCSNHCH₃, -CH₂NHCSOC₃H₇,



52. Cl, NO₂, CF₃, CH₂OH, Br, F, I, methyl, ethyl, n-propyl,
 isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-
 pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl,
 15 cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-
 oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-
 dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo,
 difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-
 difluorobutyl and 1,1-difluoropentyl; wherein each of R³
 20 through 11 is hydrido, with the proviso that at least one
 of R⁵, R⁶, R⁸ and R⁹ is an acidic group selected from CO₂H,
 SH, PO₃H₂, SO₃H, CONHNH₂, CONHNHSO₂CF₃, OH,



and



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wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

- 5 with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;


- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.



52. The composition of Claim 51 wherein m is one; wherein R^0 is selected from C_4H_9 (n), $CH_3CH_2CH=CH$,

C_3H_7 (N), SC_3H_7 , , , C_2H_5 , C_5H_{11} (n),

- 15 C_6H_{13} (n), SC_4H_9 , - CH_2S , $CH_3CH=CH$ and $CH_3CH_2CH_2CH=CH$ -

; wherein R^1 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH , CH_2OCOCH_3 , CH_2Cl , Cl, CH_2OCH_3 , $CH_2OCH(CH_3)_2$, I, CHO, CH_2CO_2H , $CH(CH_3)CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$,

- 20 $-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2$ -, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2 -adamantyl, $-CH_2NHCO_2$ -(1-naphthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$ -(1-naphthyl), $-CH_2NHCONH$ -(1-

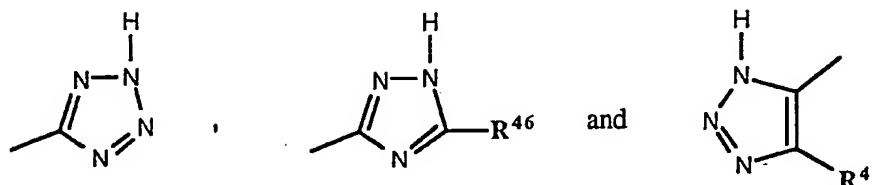
- 25 adamantyl), CO_2H , $-CH_2CH_2-CO-N$ -, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2CH_2CH_2F$, $-CH_2SH$ and $-CH_2O$ -;

- wherein R^2 is selected from H, Cl, NO_2 , CF_3 , CH_2OH , Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, 30 phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl;

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wherein each of R^3 through R^{11} is hydrido, with the proviso that at least one of R^5 , R^6 , R^8 and R^9 is an acidic group selected from CO_2H , SH , PO_3H_2 , SO_3H , $CONHNH_2$, $CONHNHSO_2CF_3$, OH ,

5



wherein each of R^{46} and R^{47} is independently selected from Cl , CN , NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

10

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

15

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.




53. The composition of Claim 51 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH=CH$, $C_3H_7(N)$, SC_3H_7 , , , C_2H_5 , $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9 , , $CH_3CH=CH$ and $CH_3CH_2CH_2CH=CH$;

wherein R^1 is selected from H , Cl , NO_2 , CF_3 , CH_2OH , Br , F , I , methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl; wherein R^2 is selected from amino, aminomethyl, aminoethyl,

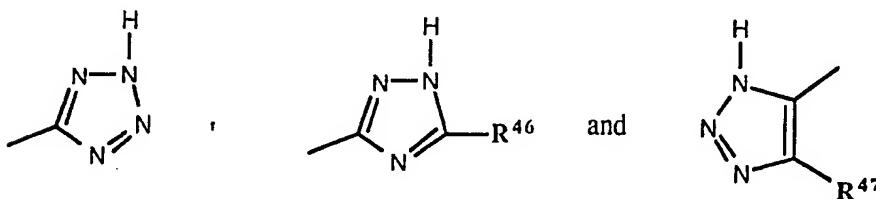
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aminopropyl, CH_2OH , $\text{CH}_2\text{OCOCH}_3$, CH_2Cl , Cl , CH_2OCH_3 ,
 $\text{CH}_2\text{OCH}(\text{CH}_3)_2$, I , CHO ,
 $\text{CH}_2\text{CO}_2\text{H}$, $\text{CH}(\text{CH}_3)\text{CO}_2\text{H}$, CO_2CH_3 , CONH_2 , CONHCH_3 ,
 $\text{CON}(\text{CH}_3)_2$,

- 5 $-\text{CH}_2-\text{NHCO}_2\text{C}_2\text{H}_5$, $-\text{CH}_2\text{NHCO}_2$ -, $-\text{CH}_2\text{NHCO}_2\text{CH}_3$, -
 $\text{CH}_2\text{NHCO}_2\text{C}_3\text{H}_7$,
 $-\text{CH}_2\text{NHCO}_2\text{CH}_2(\text{CH}_3)_2$, $-\text{CH}_2\text{NHCO}_2\text{C}_4\text{H}_9$, CH_2NHCO_2 -adamantyl,
 $-\text{CH}_2\text{NHCO}_2$ -(1-naphthyl), $-\text{CH}_2\text{NHCONHCH}_3$, $-\text{CH}_2\text{NHCONHC}_2\text{H}_5$,
 $-\text{CH}_2\text{NHCONHC}_3\text{H}_7$, $-\text{CH}_2\text{NHCONHC}_4\text{H}_9$, $-\text{CH}_2\text{NHCONHCH}(\text{CH}_3)_2$,
10 $-\text{CH}_2\text{NHCONH}$ (1-naphthyl), $-\text{CH}_2\text{NHCONH}$ (1-adamantyl), CO_2H ,
 $-\text{CH}_2\text{CH}_2\text{CO}-\text{N}$ , $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$, $-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{OCONHCH}_3$, -
 $\text{CH}_2\text{CH}_2\text{CH}_2\text{F}$, $-\text{CH}_2\text{SH}$ and $-\text{CH}_2\text{O}$ -;

- wherein each of R^3 through 11 is hydrido, with the proviso
that at least one of R^5 , R^6 , R^8 and R^9 is an acidic group
15 selected from CO_2H , SH , PO_3H_2 , SO_3H , CONHNH_2 , $\text{CONHNHSO}_2\text{CF}_3$,
 OH ,



- 20 wherein each of R^{46} and R^{47} is independently selected from
 Cl , CN , NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

- with the proviso that at least one of said R^1 through R^{11}
substituents contains a terminal primary or secondary amino
25 moiety or a moiety convertible to a primary or secondary
amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt
thereof.

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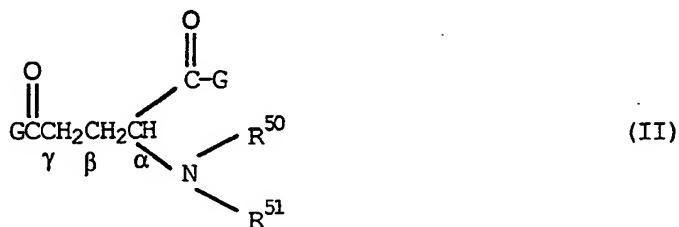
54. The composition of Claim 43 wherein said
second residue forms a kidney-enzyme-cleavable amide bond

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with the residue of said angiotensin II antagonist compound.

55. The composition of Claim 54 wherein said
5 second residue is provided by a compound of Formula II:



- wherein each of R^{50} and R^{51} may be independently selected
10 from hydrido, alkylcarbonyl, alkoxy carbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-\text{OR}^{52}$, $-\text{SR}^{53}$ and
 $\begin{array}{c} \diagup \\ \text{NR}^{54} \end{array}$ with each of R^{52} , R^{53} and R^{54} independently
 selected from hydrido and alkyl; with the proviso that said
 15 Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

56. The composition of Claim 55 wherein each G
20 substituent is hydroxy.

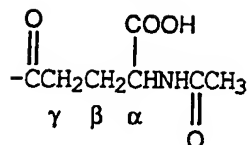
57. The composition of Claim 56 wherein each G
substituent is hydroxy; wherein R^{50} is hydrido; and wherein
 R^{51} is selected from
 25

$\begin{array}{c} \text{O} \\ \parallel \\ -\text{CR}^{55} \end{array}$ wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

58. The composition of Claim 57 wherein said
30 second residue is

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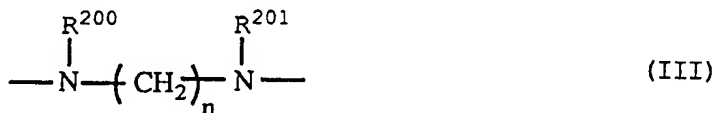


59. The composition of Claim 43 wherein said first residue is an angiotensin II antagonist compound containing a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

60. The composition of Claim 43 wherein said first residue is an angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

61. The composition of Claim 60 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

62. The composition of Claim 61 wherein said diamino-terminated linker group is a divalent radical of Formula III:



wherein each of R²⁰⁰ and R²⁰¹ may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino,

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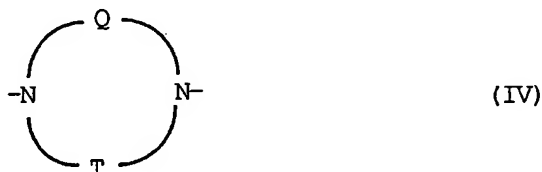
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monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

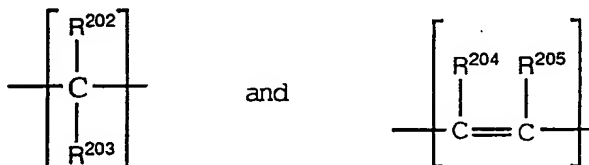
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63. The composition of Claim 62 wherein each of R²⁰⁰ and R²⁰¹ is hydrido.

64. The composition of Claim 61 wherein said
10 diamino-terminated linker group is a divalent radical of Formula IV:



15 wherein each of Q and T is one or more groups independently selected from

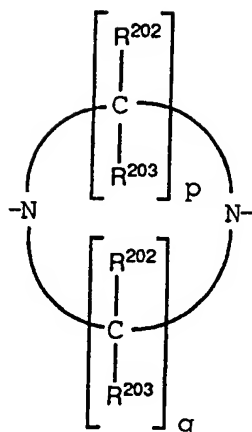


20 wherein each of R²⁰² through R²⁰⁵ is independently selected from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl, haloalkyl, hydroxyalkyl, halo, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl,
25 alkanoyl, alkenyl, cycloalkenyl and alkynyl.

30

65. The composition of Claim 64 wherein said diamino-terminated linker group is a divalent radical of Formula V:

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(V)

wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

66. The composition of Claim 65 wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

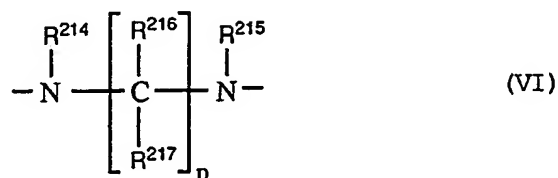
67. The composition of Claim 66 wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

68. The composition of Claim 67 wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two.

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69. The composition of Claim 61 wherein said diamino-terminated linker group is a divalent radical of Formula VI:

5



wherein each of R²¹⁴ through R²¹⁷ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, 10 monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

15

70. The composition of Claim 69 wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R²¹⁶ and R²¹⁷ is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and 20 carboxyalkyl; and wherein p is two or three.

71. The composition of Claim 70 wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R²¹⁶ and R²¹⁷ is independently selected from hydrido and alkyl; and wherein 25 p is two.

72. The composition of Claim 71 wherein each of R²¹⁴, R²¹⁵, R²¹⁶ and R²¹⁷ is hydrido; and wherein p is two.

30 73. The composition of Claim 52 wherein said angiotensin II antagonist compound is 4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

74. The composition of Claim 73 wherein said conjugate is N-acetyl-L-glutamic acid, 5-[[4'-(2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl)[1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

5

75. The composition of Claim 73 wherein said conjugate is N²-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine.

10

76. The composition of Claim 73 which is N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide.

15

77. The composition of Claim 53 wherein said angiotensin II antagonist compound is 4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

20

78. The composition of Claim 77 which is N-acetyl-L-glutamic acid, 5-[[4'-(2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl)[1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

25

79. The composition of Claim 77 which is N²-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine.

30

80. The composition of Claim 77 which is N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide.

35

81. A method for treating a hypertensive-related disorder or a sodium-retaining disorder, said method comprising administering to a patient afflicted with

or susceptible to said disorder a therapeutically-effective amount of a renal-selective conjugate, said conjugate comprising a residue of an angiotensin II antagonist compound.

5

82. The method of Claim 81 wherein said conjugate comprises a first residue and a second residue, said first and second residues connected together by a cleavable bond, wherein said first residue is provided by an angiotensin II antagonist compound, and wherein said second residue is capable of being cleaved from said first residue.

10

83. The method of Claim 82 wherein said first and second residues are provided by precursor compounds wherein the precursor compound of one of said first and second residues has a reactable carboxylic acid moiety and the precursor of the other of said first and second residues has a reactable amino moiety or a moiety convertible to a reactable amino moiety, whereby a cleavable bond may be formed between said carboxylic acid moiety and said amino moiety.

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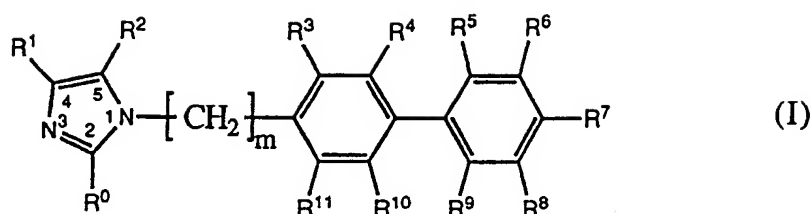
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84. The method of Claim 83 wherein said angiotensin II antagonist compound providing said first residue is selected from biphenylmethyl 1H-substituted-1,3-imidazole compounds.

25

85. The method of Claim 84 wherein said angiotensin II antagonist compound is selected from a class of compounds defined by Formula I:

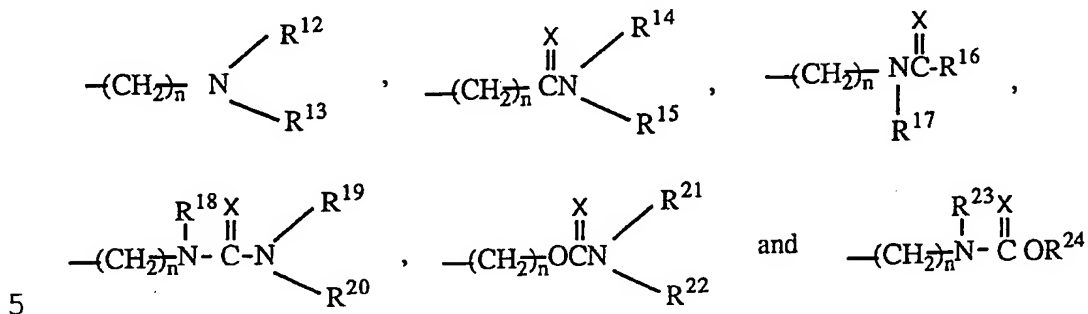
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wherein m is a number selected from one to four, inclusive;

- 5 wherein each of R⁰ through R¹¹ is independently selected from hydrido, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, formyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkenyl, 10 cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, 15 alkylthio, cycloalkylthio, alkylthiocarbonyl, alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, 20 arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio, aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, alkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, 25 alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cyclohetero-containing 30 groups has one or more ring atoms selected from oxygen,

sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is oxygen atom or sulfur atom;

10 wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, 15 monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{16} and R^{17} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form a heterocyclic group 20 having five to seven ring members including the nitrogen atom of said amino or amido radical and which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially 25 unsaturated; wherein R^{12} and R^{13} taken together, R^{14} and R^{15} taken together, R^{19} and R^{20} taken together and R^{21} and R^{22} taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical and which aromatic 30 heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

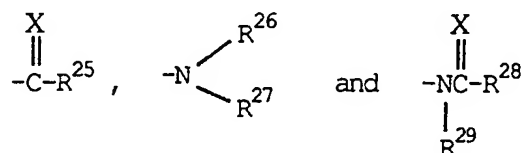
and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

5



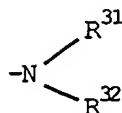
wherein n is a number selected from zero through three, inclusive, and wherein A is an acidic group selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein any of the foregoing R^1 through R^{24} , Y and A groups having a substitutable position may be substituted with one or more groups selected from hydroxy, alkyl, alkenyl, alkynyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, oxo, alkoxy, aryloxy, aralkoxy, aralkylthio, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, aryl, aroyl, cycloalkenyl, cyano, cyanoamino, nitro, alkylcarbonyloxy, alkoxy carbonyloxy, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercapto, mercaptocarbonyl, alkylthio, arylthio, alkylthiocarbonyl, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms, and amino and amido radicals of the formula



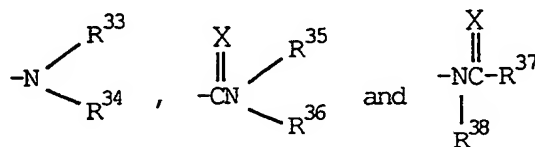
wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, DR^{30} and

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- wherein D is selected from oxygen atom and sulfur atom and
 5 R³⁰ is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R²⁵, R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkylcarbonyl, alkoxy-
 10 carbonyl, carboxyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is further independently selected from amino and amido radicals of the formula

15



wherein X is oxygen atom or sulfur atom;

- 20 wherein each of R³³, R³⁴, R³⁵, R³⁶, R³⁷ and R³⁸ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein R²⁶ and
 25 R²⁷ taken together and R²⁸ and R²⁹ taken together may each form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino or amido radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen
 30 and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R²⁶ and R²⁷ taken together and R³¹ and R³² taken together may each form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino or amido radical

and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms;

- 5 with the proviso that at least one of said R^1 through R^{24} , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

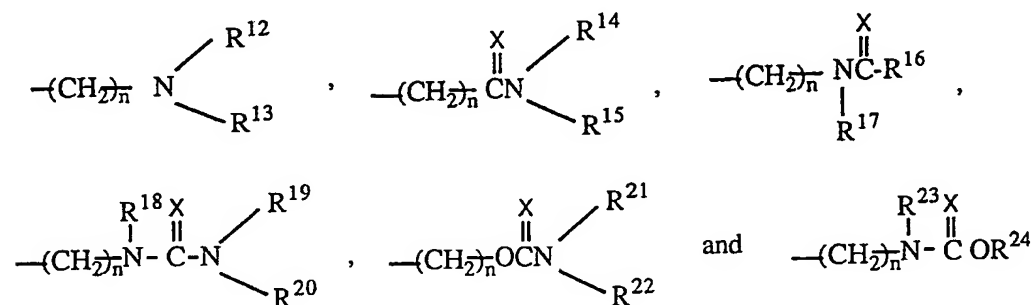
86. The method of Claim 85 wherein m is one; wherein each of R^0 through R^{11} is independently selected
- 15 from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxyalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl,
- 20 alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxyalkyl, aralkoxyalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptothiocarbonyl, mercaptoalkyl, alkoxyalkyl, alkylthio, cycloalkylthio, alkylthiocarbonyl,
- 25 alkylcarbonylthio, alkylthiocarbonyloxy, alkylthiocarbonylthio, alkylthiothiocarbonyl, alkylthiothiocarbonylthio, arylthio, arylthiocarbonyl, arylcarbonylthio, arylthiocarbonyloxy, arylthiocarbonylthio, arylthiothiocarbonyl, arylthiothiocarbonylthio,
- 30 aralkylthio, aralkylthiocarbonyl, aralkylcarbonylthio, aralkylthiocarbonyloxy, aralkylthiocarbonylthio, aralkylthiocarbonyl, aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido,
- 35 phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has

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one or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula

5



wherein X is selected from oxygen atom or sulfur atom;

10

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

15

and wherein each of R^3 through R^{11} may be further independently selected from hydrido and haloalkyl, and from acidic moieties of the formula

20



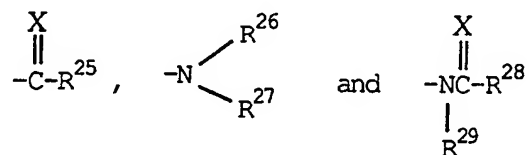
wherein n is a number selected from zero through three, inclusive; wherein A is an acidic group selected from acids containing one or more atoms selected from oxygen, sulfur, phosphorus and nitrogen atoms, and wherein said acidic group is selected to contain at least one acidic hydrogen atom, and the amide, ester and salt derivatives of said acidic moieties; wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl,

25

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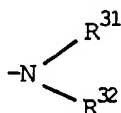
cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

- 5 and wherein any of the foregoing R^1 through R^{24} , Y and A groups having a substitutable position may be substituted with one or more groups selected from alkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, difluoroalkyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, 10 alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



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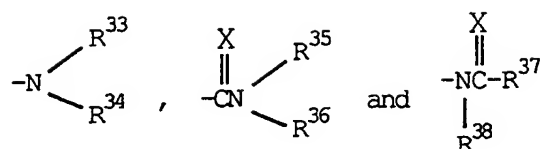
wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl, and DR^{30} and



20

- wherein D is selected from oxygen atom and sulfur atom, and R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl; wherein each of R^{26} , 25 R^{27} , R^{28} , R^{29} , R^{31} and R^{32} is independently selected from hydrido, alkyl, cycloalkyl, cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, alkanoyl, alkoxy carbonyl, carboxyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl, and wherein each of R^{26} , R^{27} , R^{28} , R^{29} , R^{31} and R^{32} 30 is further independently selected from amino and amido radicals of the formula

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wherein X is selected from oxygen atom or sulfur atom;

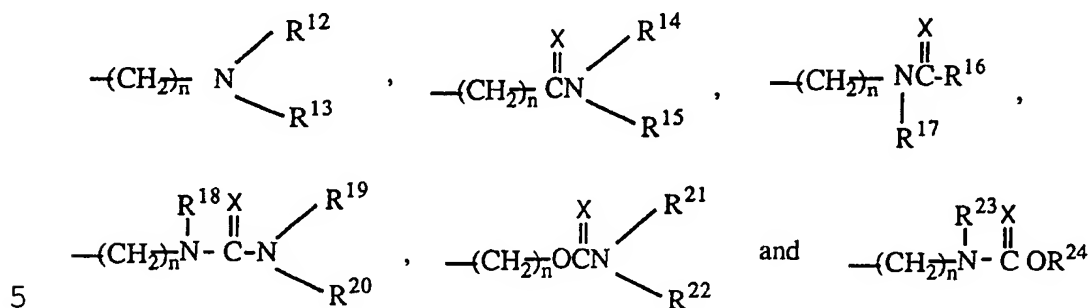
- 5 wherein each of R²⁶ through R³¹ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;
- 10 with the proviso that at least one of said R¹ through R²⁴, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 15 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

87. The method of Claim 86 wherein m is one;
- 20 wherein each of R⁰ through R¹¹ is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, mercaptocarbonyl, alkoxy carbonyloxy, alkylcarbonyloxyalkyl, alkoxy carbonylalkyl, aralkoxy carbonylalkyl, aralkylcarbonyloxyalkyl, alkylthio, cycloalkylthio, arylthio, aralkylthio,
- 25 aralkylthiocarbonylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl
- 30 wherein each of said heteroaryl- and cycloheteroalkyl- containing groups has one or more hetero ring atoms
- 35

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selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom or sulfur atom;

10 wherein each n is a number independently selected from zero to six, inclusive;

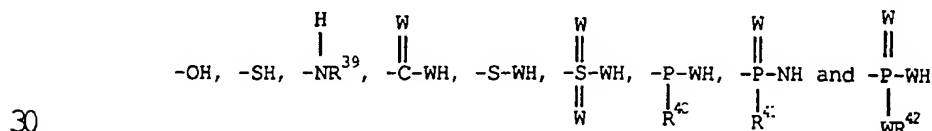
wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, 15 monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from hydrido and haloalkyl, 20 and from acidic moieties of the formula



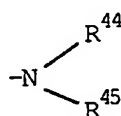
wherein n is a number selected from zero through three, 25 inclusive;

wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



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wherein each W is independently selected from oxygen atom, sulfur atom and NR⁴³; wherein each of R³⁹, R⁴⁰, R⁴¹, R⁴² and R⁴³ is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, cycloalkylalkyl, aryl and aralkyl; wherein each of R³⁹, R⁴⁰, R⁴¹ and R⁴² may be further independently selected from amino radicals of the formula



10

wherein each of R⁴⁴ and R⁴⁵ is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein R⁴⁴ and R⁴⁵ taken together may form a heterocyclic group having five to seven ring members including the nitrogen atom of said amino radical, which heterocyclic group may further contain one or more hetero atoms as ring members selected from oxygen, nitrogen and sulfur atoms and which heterocyclic group may be saturated or partially unsaturated; wherein R⁴⁴ and R⁴⁵ taken together may form an aromatic heterocyclic group having five ring members including the nitrogen atom of said amino radical and which aromatic heterocyclic group may further contain one or more hetero atoms as ring atoms selected from oxygen, nitrogen and sulfur atoms; wherein each of R⁴⁰ and R⁴¹ may be further independently selected from hydroxy, alkoxy, alkylthio, aryloxy, arylthio, aralkylthio and aralkoxy; and the amide, ester and salt derivatives of said acidic groups;

30

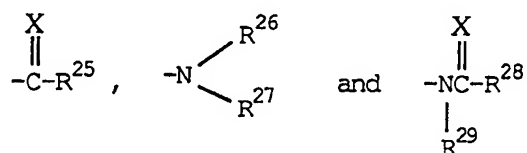
wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which heterocyclic ring contains at least one hetero atom selected from oxygen, sulfur and nitrogen atoms, which

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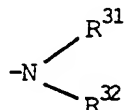
heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

and wherein any of the foregoing R^1 through R^{24} , Y and A groups having a substitutable position may be substituted by one or more groups selected from alkyl, difluoroalkyl, alkenyl, aralkyl, hydroxyalkyl, trifluoromethyl, alkoxy, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, carboxyl, mercaptocarbonyl, alkylthio, alkylthiocarbonyl, and amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom; wherein R^{25} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, aryl and DR^{30} and



wherein D is selected from oxygen atom and sulfur atom, wherein R^{30} is selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, aralkyl and aryl;

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wherein each of R²⁶, R²⁷, R²⁸, R²⁹, R³¹ and R³² is
independently selected from hydrido, alkyl, cycloalkyl,
cyano, hydroxyalkyl, haloalkyl, cycloalkylalkyl,
5 alkoxyalkyl, alkanoyl, alkoxycarbonyl, carboxyl,
haloalkylsulfinyl, haloalkylsulfonyl, aralkyl and aryl;

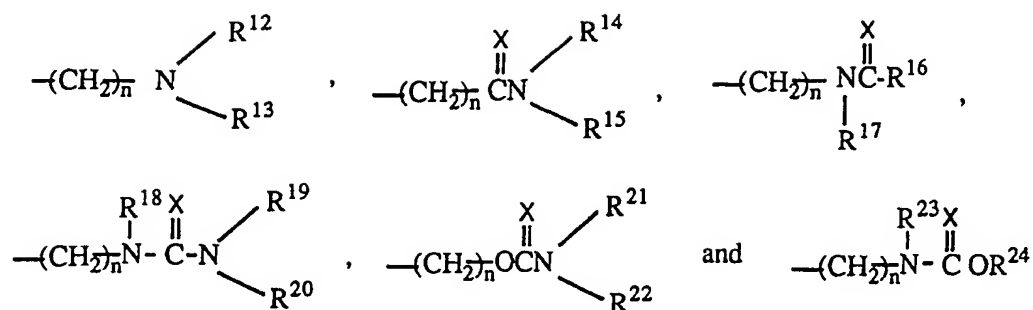
with the proviso that at least one of said R¹ through R²⁴,
Y and A substituents contains a terminal primary or
10 secondary amino moiety or a moiety convertible to a primary
or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt
thereof.

15

88. The method of Claim 87 wherein m is one;
wherein each of R⁰, R¹ and R² is independently selected
from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl,
cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy,
20 aryloxyalkyl, aralkoxy, alkoxyalkyl, alkylcarbonyl,
alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl,
cycloalkynyl, cyano, nitro, carboxyl, carboxyalkyl,
alkylcarbonyloxy, alkylcarbonyloxyalkyl,
alkoxycarbonylalkyl, aralkoxycarbonylalkyl,
25 aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl,
alkoxycarbonyloxy, alkylthio, cycloalkylthio, arylthio,
aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl,
aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl,
arylsulfonyl, phthalimido, phthalimidoalkyl, heteroaryl,
30 heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl
and cycloheteroalkylcarbonylalkyl wherein each of said
heteroaryl- and cycloheteroalkyl-containing groups has one
or more hetero ring atoms selected from oxygen, sulfur and
nitrogen atoms, and wherein each of R⁰ through R¹¹ may be
35 further independently selected from amino and amido
radicals of the formula

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wherein X is selected from oxygen atom and sulfur atom;

5

wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R¹² through R²⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, monoalkylamino, dialkylamino, hydroxyalkyl, cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl;

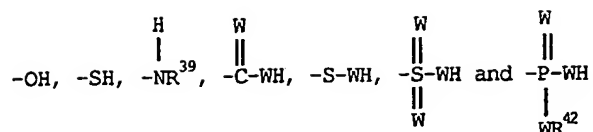
wherein each of R³ through R¹¹ is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, aroyl, aryloxy, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxyalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, cyano, nitro, carboxyl, alkylthio, aralkylthio, mercapto, alkylsulfinyl, alkylsulfonyl, aralkylsulfinyl, aralkylsulfonyl, arylsulfinyl, arylsulfonyl and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

and wherein each of R³ through R¹¹ may be an acidic moiety further independently selected from acidic moieties of the formula

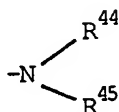


wherein n is a number selected from zero through three, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from

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wherein each W is independently selected from oxygen atom,
 5 sulfur atom and NR^{43} ; wherein each of R^{39} , R^{42} and R^{43} is
 independently selected from hydrido, alkyl, haloalkyl,
 haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl,
 cycloalkylalkyl, aryl and aralkyl; wherein each of R^{39} and
 10 R^{42} may be further independently selected from amino
 radical of the formula



wherein each of R^{44} and R^{45} is independently selected from
 15 hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl,
 cycloalkylalkyl, alkoxyalkyl, aralkyl and aryl, and wherein
 R^{44} and R^{45} taken together may form a heterocyclic group
 having five to seven ring members including the nitrogen
 atom of said amino radical, which heterocyclic group may
 20 further contain one or more hetero atoms as ring members
 selected from oxygen, nitrogen and sulfur atoms, and which
 heterocyclic group may be saturated or partially
 unsaturated; wherein R^{44} and R^{45} taken together may form an
 aromatic heterocyclic group having five ring members
 25 including the nitrogen atom of said amino radical and which
 aromatic heterocyclic group may further contain one or more
 hetero atoms as ring atoms selected from oxygen, nitrogen
 and sulfur atoms; and the amide, ester and salt derivatives
 of said acidic groups; wherein said bioisostere of
 30 carboxylic acid may be further selected from heterocyclic
 acidic groups consisting of heterocyclic rings of four to
 about nine ring members, which ring contains at least one
 hetero atom, selected from oxygen, sulfur and nitrogen
 atoms, which heterocyclic ring may be saturated, fully
 35 unsaturated or partially unsaturated, and which

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heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of the phenyl rings of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, aryl and aralkyl;

wherein each of R^1 through R^{24} , Y and A independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and aralkoxy;

with the proviso that at least one of said R^1 through R^{24} , Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

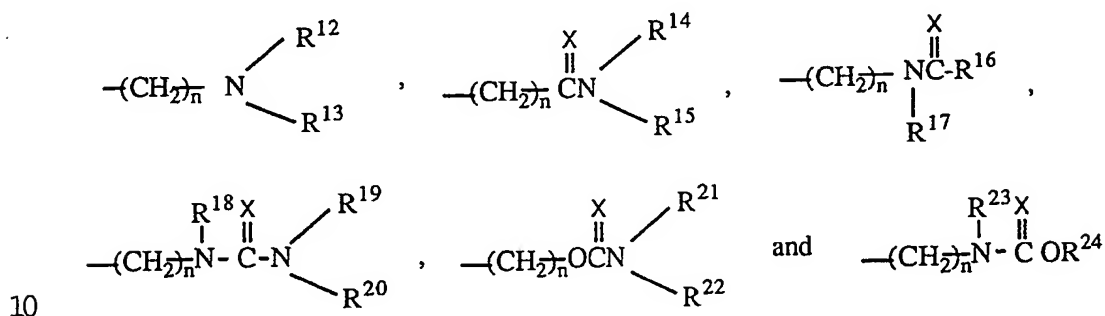
or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

89. The method of Claim 88 wherein m is one; wherein each of R^0 , R^1 and R^2 is independently selected from alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, alkylcarbonyl, alkoxycarbonyl, alkenyl, cycloalkyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, mercaptocarbonyl, mercaptoalkyl, alkoxycarbonyloxy, alkylthio, cycloalkylthio, phthalimido,

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phthalimidoalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl and cycloheteroalkylcarbonylalkyl wherein each of said heteroaryl- and cycloheteroalkyl-containing groups has one
 5 or more hetero ring atoms selected from oxygen, sulfur and nitrogen atoms, and wherein each of R^0 through R^{11} may be further independently selected from amino and amido radicals of the formula



wherein X is selected from oxygen atom and sulfur atom;

15 wherein each n is a number independently selected from zero to six, inclusive;

wherein each of R^{12} through R^{24} is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino,
 20 hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

wherein each of R^3 through R^{11} is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl,
 25 phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, alkylcarbonyl, alkoxy carbonyl, alkenyl, cyano, nitro, carboxyl, alkylthio, mercapto and heteroaryl having one or more ring atoms selected from oxygen, sulfur and nitrogen atoms;

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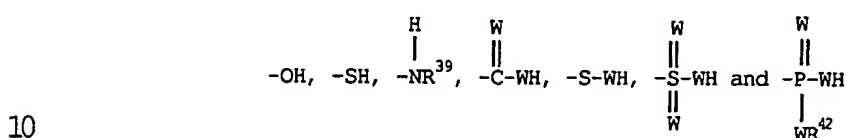
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and wherein each of R^3 through R^{11} may be an acidic moiety further independently selected from acidic moieties of the formula



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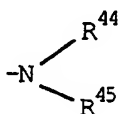
wherein n is a number selected from zero through two, inclusive; wherein A is selected from carboxylic acid and bioisosteres of carboxylic acid selected from



10

wherein each W is independently selected from oxygen atom, sulfur atom and NR^{43} ; wherein each of R^{39} , R^{42} and R^{43} is independently selected from hydrido, alkyl, haloalkyl, haloalkylsulfonyl, haloalkylcarbonyl, cycloalkyl, phenyl and benzyl; wherein each of R^{39} and R^{42} may be further independently selected from amino radical of the formula

15



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wherein each of R^{44} and R^{45} is independently selected from hydrido, alkyl, cycloalkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, benzyl and phenyl; and the amide, ester and salt derivatives of said acidic groups;

25

wherein said bioisostere of carboxylic acid may be further selected from heterocyclic acidic groups consisting of heterocyclic rings of four to about nine ring members, which ring contains at least one hetero atom, selected from oxygen, sulfur and nitrogen atoms, which heterocyclic ring may be saturated, fully unsaturated or partially unsaturated, and which heterocyclic ring may be attached at a single position selected from R^3 through R^{11} or may be attached at any two adjacent positions selected from R^3 through R^{11} so as to form a fused-ring system with one of

35

the phenyl rings of the biphenyl moiety of Formula I; and the amide, ester and salt derivatives of said heterocyclic acidic groups;

- 5 wherein Y is a spacer group independently selected from one or more of alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, phenyl, phenalkyl and aralkyl;

- 10 wherein each of R¹ through R²⁴, Y and A and independently may be substituted at any substitutable position with one or more groups selected from alkyl, cycloalkyl, cycloalkylalkyl, hydroxy, oxo, trifluoromethyl, difluoroalkyl, alkoxycarbonyl, cyano, nitro, alkylsulfonyl, haloalkylsulfonyl, aryl, aralkyl, alkoxy, aryloxy and
15 aralkoxy;

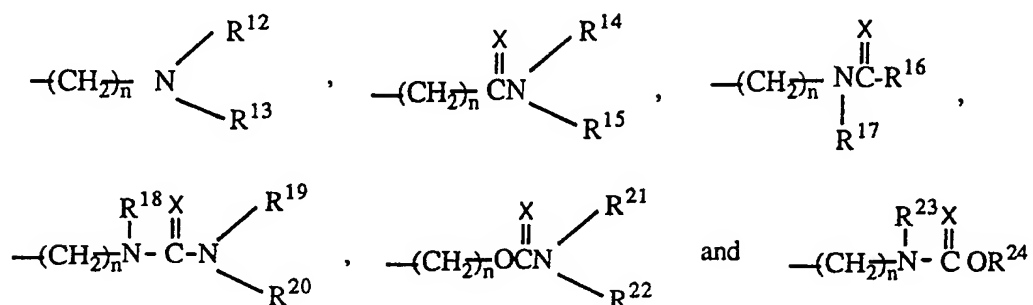
- with the proviso that at least one of said R¹ through R²⁴, Y and A substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary
20 or secondary amino moiety;

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

- 25 90. The method of Claim 89 wherein m is one; wherein R⁰ is selected from alkyl, alkenyl, phenyl, alkylthio, cycloalkyl, cycloalkylalkyl and cycloalkylthio; wherein each of R¹ and R² is independently selected from alkyl, aminoalkyl, hydroxyalkyl, halo, haloalkyl,
30 cycloalkyl, cycloalkylalkyl, alkoxy, aralkyl, aryl, benzoyl, phenoxy, phenoxyalkyl, phenalkyloxy, phenylthio, phenalkylthio, aralkoxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cycloalkenyl, alkynyl, cyano, nitro, carboxyl, carboxyalkyl, alkylcarbonyloxy,
35 mercaptoalkyl, mercaptocarbonyl, alkoxycarbonyloxy, alkylcarbonyloxyalkyl, alkoxycarbonylalkyl, aralkoxycarbonylalkyl, aralkylcarbonyloxyalkyl, phthalimido, phthalimidoalkyl, imidazoalkyl, tetrazole,

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tetrazolealkyl, alkylthio, cycloalkylthio, and amino and amido radicals of the formula



5

wherein X is selected from oxygen atom and sulfur atom;

wherein each n is a number independently selected from zero to six, inclusive;

10

wherein each of R¹² through R²⁴ is independently selected from hydrido, alkyl, cycloalkyl, cyano, amino, hydroxyalkyl, alkoxyalkyl, phenalkyl and phenyl;

15

wherein each of R³ through R¹¹ is independently selected from hydrido, hydroxy, alkyl, hydroxyalkyl, halo, haloalkyl, cycloalkyl, cycloalkylalkyl, alkoxy, phenalkyl, phenyl, benzoyl, phenoxy, phenalkyloxy, alkoxyalkyl, acetyl, alkoxycarbonyl, alkenyl, cyano, nitro, carboxyl,

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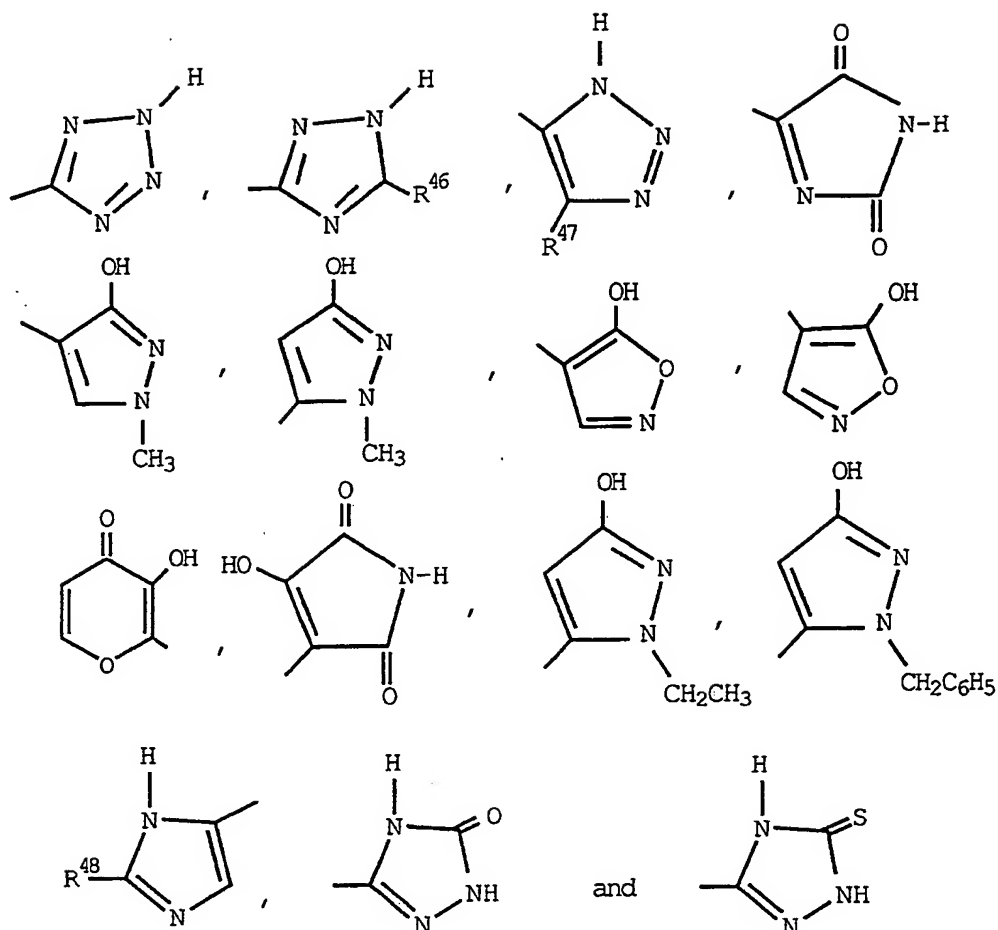
alkylthio and mercapto;

and wherein each of R³ through R¹¹ may be an acidic moiety further independently selected from acidic moieties consisting of CO₂H, CO₂CH₃, SH, CH₂SH, C₂H₄SH, PO₃H₂,

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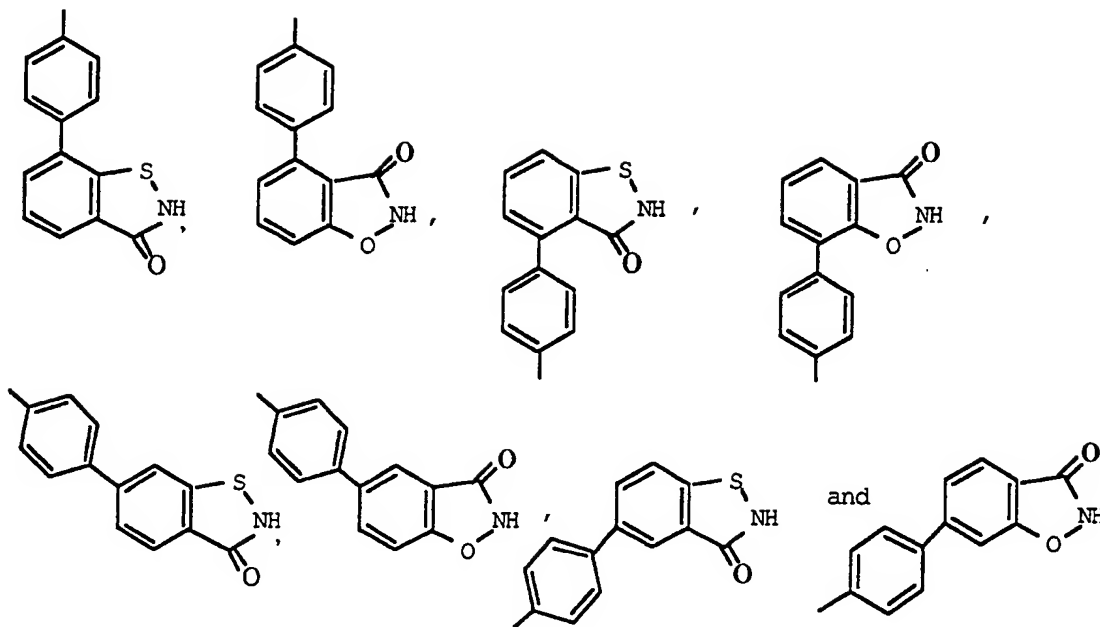
NHSO₂CF₃, NHSO₂C₆F₅, SO₃H, CONHNH₂, CONHNHSO₂CF₃, CONHOCH₃, CONHOC₂H₅, CONHCF₃, OH, CH₂OH, C₂H₄OH, OPO₃H₂, OSO₃H,

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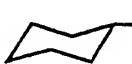

- wherein each of R⁴⁶, R⁴⁷ and R⁴⁸ is independently selected
 5 from H, Cl, CN, NO₂, CF₃, C₂F₅, C₃F₇, CHF₂, CH₂F, CO₂CH₃,
 CO₂C₂H₅, SO₂CH₃, SO₂CF₃ and SO₂C₆F₅; wherein Z is selected
 from O, S, NR⁴⁹ and CH₂; wherein R⁴⁹ is selected from
 hydrido, CH₃ and CH₂C₆H₅; and wherein said acidic moiety
 may be a heterocyclic acidic group attached at any two
 10 adjacent positions of R³ through R¹¹ so as to form a fused
 ring system so as to include one of the phenyl rings of the
 biphenyl moiety of Formula I, said biphenyl fused ring
 system selected from

365



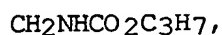
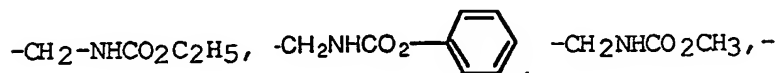
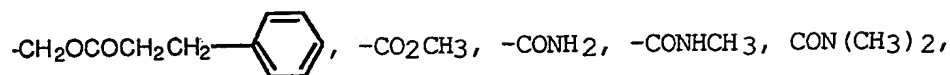
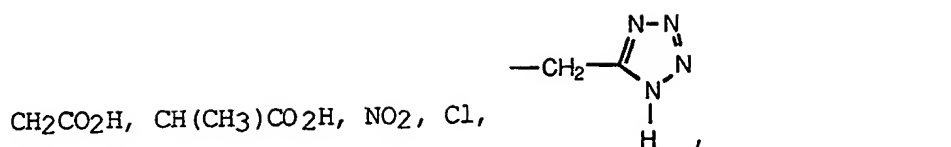
and the esters, amides and salts of said acidic moieties;

- 5 with the proviso that at least one of said R^1 through R^{24} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;
- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

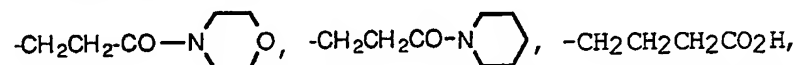
91. The method of Claim 90 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH=CH$, $C_3H_7(N)$,
 15 SC_3H_7 ,  CH_2 , , C_2H_5 , $C_5H_{11}(n)$, $C_6H_{13}(n)$,
 SC_4H_9 ,  CH_2S , $CH_3CH=CH$ and $CH_3CH_2CH_2CH=CH-$; wherein
 each of R^1 and R^2 is independently selected from amino,
 aminomethyl, aminoethyl, aminopropyl, CH_2OH , CH_2OCOCH_3 ,
 CH_2Cl , Cl , CH_2OCH_3 , $CH_2OCH(CH_3)_2$, I , CHO ,

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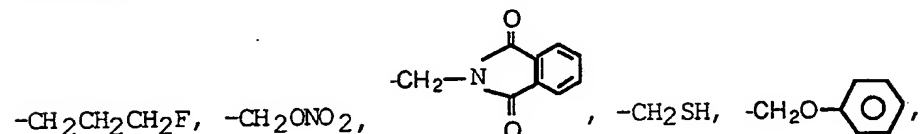
366



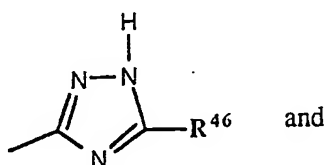
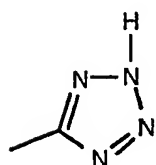
- 5 -CH₂NHCO₂CH₂(CH₃)₂, -CH₂NHCO₂C₄H₉, CH₂NHCO₂-adamantyl,
 -CH₂NHCO₂-(1-naphthyl), -CH₂NHCONHCH₃, -CH₂NHCONHC₂H₅,
 -CH₂NHCONHC₃H₇, -CH₂NHCONHC₄H₉, -CH₂NHCONHCH(CH₃)₂,
 -CH₂NHCONH(1-naphthyl), -CH₂NHCONH(1-adamantyl), CO₂H,



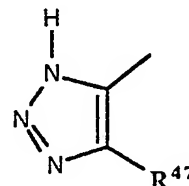
- 10 -CH₂CH₂F, -CH₂OCONHCH₃, -CH₂OCSNHCH₃, -CH₂NHCSOC₃H₇,



92. Cl, NO₂, CF₃, CH₂OH, Br, F, I, methyl, ethyl, n-propyl,
 isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-
 pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl,
 15 cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-
 oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-
 dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo,
 difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-
 difluorobutyl and 1,1-difluoropentyl; wherein each of R³
 20 through 11 is hydrido, with the proviso that at least one
 of R⁵, R⁶, R⁸ and R⁹ is an acidic group selected from CO₂H,
 SH, PO₃H₂, SO₃H, CONHNH₂, CONHNHSO₂CF₃, OH,




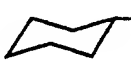
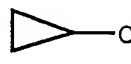



and



wherein each of R^{46} and R^{47} is independently selected from Cl, CN, NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

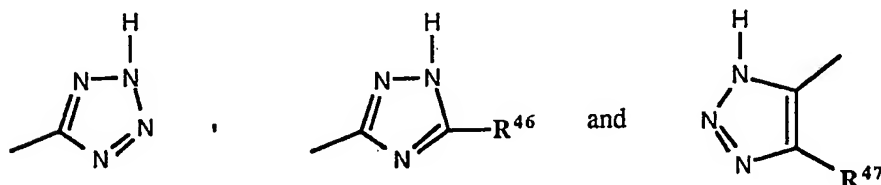
- 5 with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

- 10 or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

92. The method of Claim 91 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH=CH$, $C_3H_7(N)$, SC_3H_7 , - CH_2 , , C_2H_5 , $C_5H_{11}(n)$, $C_6H_{13}(n)$, SC_4H_9 , - CH_2S , $CH_3CH=CH$ and $CH_3CH_2CH_2CH=CH$ -; wherein R^1 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH , CH_2OCOCH_3 , CH_2Cl , Cl, CH_2OCH_3 , $CH_2OCH(CH_3)_2$, I, CHO, CH_2CO_2H , $CH(CH_3)CO_2H$, $-CO_2CH_3$, $-CONH_2$, $-CONHCH_3$, $CON(CH_3)_2$, $-CH_2-NHCO_2C_2H_5$, $-CH_2NHCO_2$ -, $-CH_2NHCO_2CH_3$, $-CH_2NHCO_2C_3H_7$, $-CH_2NHCO_2CH_2(CH_3)_2$, $-CH_2NHCO_2C_4H_9$, CH_2NHCO_2 -adamantyl, $-CH_2NHCO_2$ -(1-naphthyl), $-CH_2NHCONHCH_3$, $-CH_2NHCONHC_2H_5$, $-CH_2NHCONHC_3H_7$, $-CH_2NHCONHC_4H_9$, $-CH_2NHCONHCH(CH_3)_2$, $-CH_2NHCONH$ -(1-naphthyl), $-CH_2NHCONH$ -(1-adamantyl), CO_2H , $-CH_2CH_2CO-N$ -, $-CH_2CH_2CH_2CO_2H$, $-CH_2CH_2F$, $-CH_2OCONHCH_3$, $-CH_2CH_2CH_2F$, $-CH_2SH$ and $-CH_2O$ -;
- 20 wherein R^2 is selected from H, Cl, NO_2 , CF_3 , CH_2OH , Br, F, I, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl;
- 25
- 30

wherein each of R^3 through R^{11} is hydrido, with the proviso that at least one of R^5 , R^6 , R^8 and R^9 is an acidic group selected from CO_2H , SH , PO_3H_2 , SO_3H , $CONHNH_2$, $CONHNHSO_2CF_3$, OH ,

5



wherein each of R^{46} and R^{47} is independently selected from Cl , CN , NO_2 , CF_3 , CO_2CH_3 and SO_2CF_3 ;

10

with the proviso that at least one of said R^1 through R^{11} substituents contains a terminal primary or secondary amino moiety or a moiety convertible to a primary or secondary amino moiety;

15

or a tautomer thereof or a pharmaceutically-acceptable salt thereof.

93. The method of Claim 91 wherein m is one; wherein R^0 is selected from $C_4H_9(n)$, $CH_3CH_2CH=CH$, $C_3H_7(N)$,

20

SC_3H_7 , , , C_2H_5 , $C_5H_{11}(n)$, $C_6H_{13}(n)$,

SC_4H_9 , , $CH_3CH=CH$ and $CH_3CH_2CH_2CH=CH-$;

wherein R^1 is selected from H , Cl , NO_2 , CF_3 , CH_2OH , Br , F , I , methyl, ethyl, n -propyl, isopropyl, n -butyl, sec -butyl,

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isobutyl, $tert$ -butyl, n -pentyl, isopentyl, neopentyl, phenyl, benzyl, phenethyl, cyclohexyl, cyclohexylmethyl, 1-oxoethyl, 1-oxopropyl, 1-oxobutyl, 1-oxopentyl, 1,1-dimethoxypropyl, 1,1-dimethoxybutyl, 1,1-dimethoxypentyl, hydroxyalkyl, halo, difluoromethyl, 1,1-difluoroethyl, 1,1-difluoropropyl, 1,1-difluorobutyl and 1,1-difluoropentyl;

30

wherein R^2 is selected from amino, aminomethyl, aminoethyl, aminopropyl, CH_2OH , CH_2OCOCH_3 , CH_2Cl , Cl , CH_2OCH_3 , $CH_2OCH(CH_3)_2$, I , CHO ,


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CH₂CO₂H, CH(CH₃)CO₂H, , -CO₂CH₃, -CONH₂, -CONHCH₃,
CON(CH₃)₂,

-CH₂-NHCO₂C₂H₅, -CH₂NHCO₂-, -CH₂NHCO₂CH₃, -

CH₂NHCO₂C₃H₇,

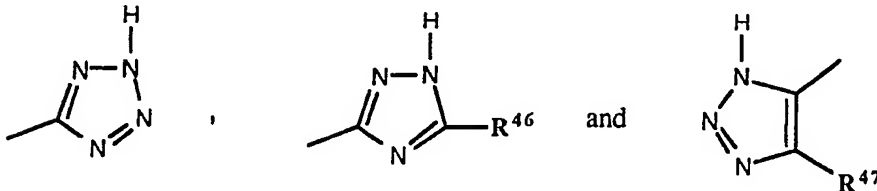
- 5 -CH₂NHCO₂CH₂(CH₃)₂, -CH₂NHCO₂C₄H₉, CH₂NHCO₂-adamantyl,
-CH₂NHCO₂-(1-naphthyl), -CH₂NHCONHCH₃, -CH₂NHCONHC₂H₅,
-CH₂NHCONHC₃H₇, -CH₂NHCONHC₄H₉, -CH₂NHCONHCH(CH₃)₂,
-CH₂NHCONH(1-naphthyl), -CH₂NHCONH(1-adamantyl), CO₂H,

-CH₂CH₂-CO-N, -CH₂CH₂CH₂CO₂H, -CH₂CH₂F, -CH₂OCONHCH₃, -

- 10 CH₂CH₂CH₂F, -CH₂SH and -CH₂O-;

wherein each of R³ through R¹¹ is hydrido, with the proviso
that at least one of R⁵, R⁶, R⁸ and R⁹ is an acidic group
selected from CO₂H, SH, PO₃H₂, SO₃H, CONHNH₂, CONHNHSO₂CF₃,
OH,

15



wherein each of R⁴⁶ and R⁴⁷ is independently selected from
Cl, CN, NO₂, CF₃, CO₂CH₃ and SO₂CF₃;

20

with the proviso that at least one of said R¹ through R¹¹
substituents contains a terminal primary or secondary amino
moiety or a moiety convertible to a primary or secondary
amino moiety;

25

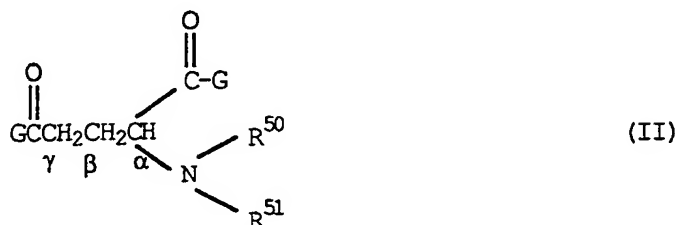
or a tautomer thereof or a pharmaceutically-acceptable salt
thereof.

94. The method of Claim 83 wherein said second
30 residue forms a kidney-enzyme-cleavable amide bond with the
residue of said angiotensin II antagonist compound.

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95. The method of Claim 94 wherein said second residue is provided by a compound of Formula II:



5

wherein each of R^{50} and R^{51} may be independently selected from hydrido, alkylcarbonyl, alkoxy carbonyl, alkoxyalkyl, hydroxyalkyl and haloalkyl; and wherein G is selected from hydroxyl, halo, mercapto, $-\text{OR}^{52}$, $-\text{SR}^{53}$ and

10

$-\text{NR}^{54}$ with each of R^{52} , R^{53} and R^{54} independently selected from hydrido and alkyl; with the proviso that said Formula II compound is selected such that formation of the cleavable amide bond occurs at carbonyl moiety attached at the gamma-position carbon of said Formula II compound.

15

96. The method of Claim 95 wherein each G substituent is hydroxy.

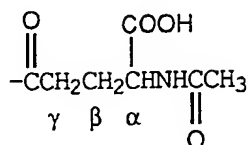
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97. The method of Claim 96 wherein each G substituent is hydroxy; wherein R^{50} is hydrido; and wherein

R^{51} is selected from $-\text{CR}^{55}$ wherein R^{55} is selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl and chloromethyl.

25

98. The method of Claim 97 wherein said second residue is



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99. The method of Claim 83 wherein said first residue is an angiotensin II antagonist compound containing a terminal primary or secondary amino moiety selected from amino and linear or branched aminoalkyl moieties containing linear or branched alkyl groups selected from aminomethyl, aminoethyl, aminopropyl, aminoisopropyl, aminobutyl, aminosecbutyl, aminoisobutyl, aminotertbutyl, aminopentyl, aminoisopentyl and aminoneopentyl.

100. The method of Claim 83 wherein said first residue is an angiotensin II antagonist compound containing a moiety convertible to a primary or secondary amino terminal moiety.

101. The method of Claim 100 wherein said moiety convertible to an amino terminal moiety is a carboxylic acid group reactable with an amino moiety of a diamino-terminated linker group to provide a terminal amino moiety which may then be further reacted with a carboxylic acid moiety of a compound providing said second residue so as to form a hydrolyzable amide bond.

102. The method of Claim 101 wherein said diamino-terminated linker group is a divalent radical of Formula III:



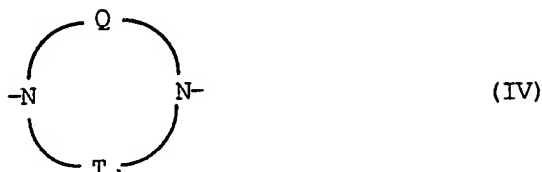
wherein each of R²⁰⁰ and R²⁰¹ may be independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein n is zero or a number selected from three through seven, inclusive.

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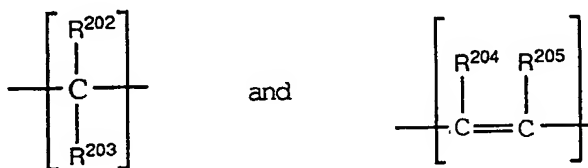
372

103. The method of Claim 102 wherein each of R^{200} and R^{201} is hydrido.

104. The method of Claim 101 wherein said
5 diamino-terminated linker group is a divalent radical of
Formula IV:



10 wherein each of Q and T is one or more groups independently
selected from

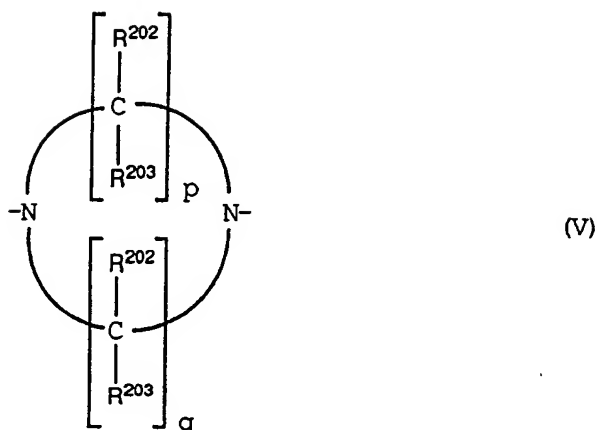


15 wherein each of R^{202} through R^{205} is independently selected
from hydrido, hydroxy, alkyl, cycloalkyl, cycloalkylalkyl,
aralkyl, aryl, alkoxy, aralkoxy, aryloxy, alkoxyalkyl,
haloalkyl, hydroxyalkyl, halo, cyano, amino,
monoalkylamino, dialkylamino, carboxy, carboxyalkyl,
20 alkanoyl, alkenyl, cycloalkenyl and alkynyl.

105. The method of Claim 104 wherein said
diamino-terminated linker group is a divalent radical of
Formula V:

25

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wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, phenalkyl, phenyl, alkoxy, benzyloxy, phenoxy, alkoxyalkyl, hydroxyalkyl, halo, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from one through six, inclusive; with the proviso that when each of R^{202} and R^{203} is selected from halo, hydroxy, amino, monoalkylamino and dialkylamino, then the carbon to which R^{202} or R^{203} is attached in Formula V is not adjacent to a nitrogen atom of Formula V.

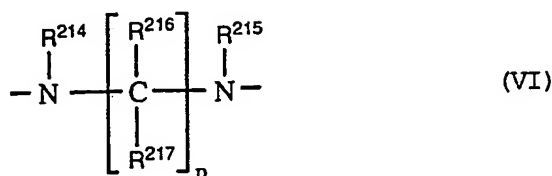
106. The method of Claim 105 wherein each of R^{202} and R^{203} is independently selected from hydrido, hydroxy, alkyl, alkoxy, amino, monoalkylamino, carboxy, carboxyalkyl and alkanoyl; and wherein each of p and q is a number independently selected from two through four, inclusive.

107. The method of Claim 106 wherein each of R^{202} and R^{203} is independently selected from hydrido, amino, monoalkylamino and carboxyl; and wherein each of p and q is independently selected from the numbers two and three.

108. The method of Claim 107 wherein each of R^{202} and R^{203} is hydrido; and wherein each of p and q is two.

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109. The method of Claim 101 wherein said diamino-terminated linker group is a divalent radical of Formula VI:



wherein each of R²¹⁴ through R²¹⁷ is independently selected from hydrido, alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, aralkyl, aryl, haloalkyl, amino, monoalkylamino, dialkylamino, cyanoamino, carboxyalkyl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl and arylsulfonyl; and wherein p is a number selected from one through six inclusive.

110. The method of Claim 109 wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R²¹⁶ and R²¹⁷ is independently selected from hydrido, alkyl, phenalkyl, phenyl, alkoxyalkyl, hydroxyalkyl, haloalkyl and carboxyalkyl; and wherein p is two or three.

111. The method of Claim 110 wherein each of R²¹⁴ and R²¹⁵ is hydrido; wherein each of R²¹⁶ and R²¹⁷ is independently selected from hydrido and alkyl; and wherein p is two.

112. The method of Claim 111 wherein each of R²¹⁴, R²¹⁵, R²¹⁶ and R²¹⁷ is hydrido; and wherein p is two.

113. The method of Claim 92 wherein said angiotensin II antagonist compound is 4'-[2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

375

114. The method of Claim 113 wherein said conjugate is N-acetyl-L-glutamic acid, 5-[[4'-(2-butyl-5-chloro-4-(hydroxymethyl)-1H-imidazol-1-ylmethyl)[1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

5

115. The method of Claim 113 wherein said conjugate is N²-acetyl-N-[[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]methyl]-L-glutamine.

10

116. The method of Claim 113 which is N-acetyl-L-glutamic acid, 5-[2-butyl-5-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-4-yl]acetylhydrazide.

15

117. The method of Claim 93 wherein said angiotensin II antagonist compound is 4'-[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl][1,1'-biphenyl]-2-carboxylic acid.

20

118. The method of Claim 117 which is N-acetyl-L-glutamic acid, 5-[[4'-(2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-ylmethyl)[1,1'-biphenyl]-2-yl]carbonyl]hydrazide.

25

119. The method of Claim 117 which is N²-acetyl-N-[[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]methyl]-L-glutamine.

30

120. The method of Claim 117 which is N-acetyl-L-glutamic acid, 5-[2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazol-5-yl]acetylhydrazide.

35

121. The method of Claim 81 wherein said hypertensive-related disorder is chronic hypertension.

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122. The method of Claim 81 wherein said
sodium-retaining disorder is congestive heart failure.

123. The method of Claim 81 wherein said
5 sodium-retaining disorder is cirrhosis.

124. The method of Claim 81 wherein said
sodium-retaining disorder is nephrosis.

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Chronic Infusion of Example #81 Conjugate

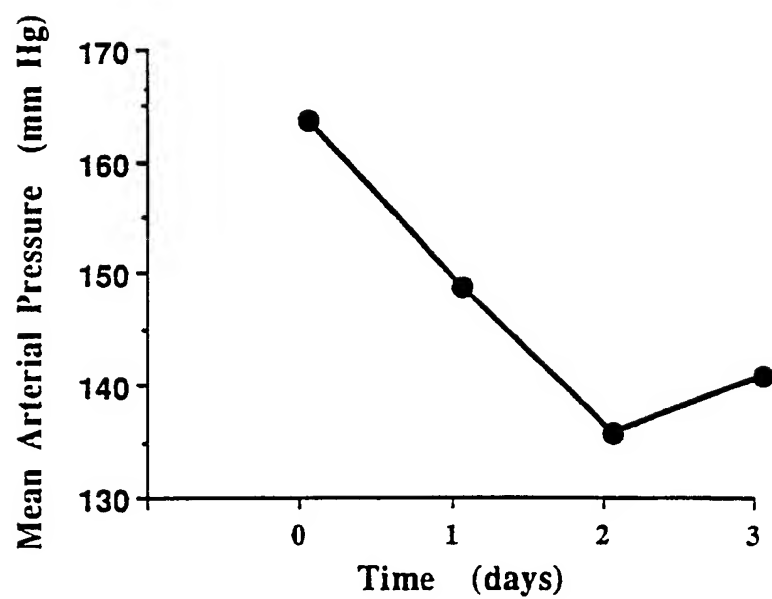


Figure 1

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Acute Angiotensin II Pressor Response During
Chronic Infusion of Example #81 Conjugate

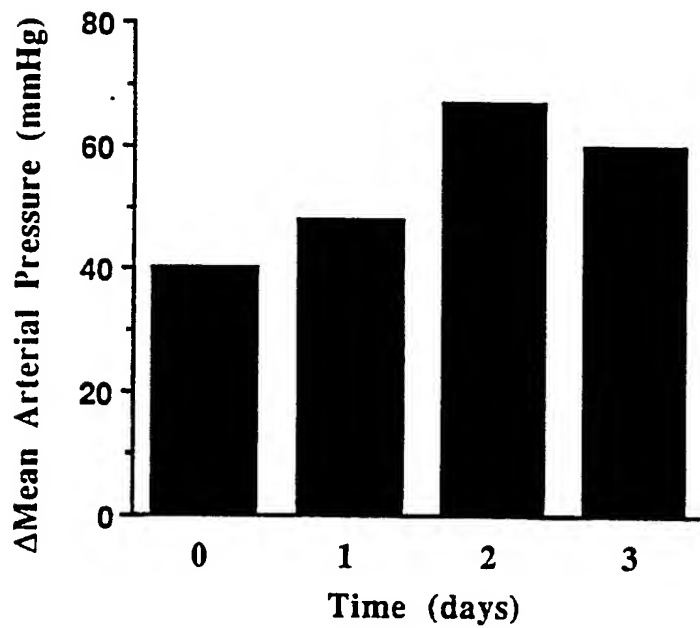


Figure 2

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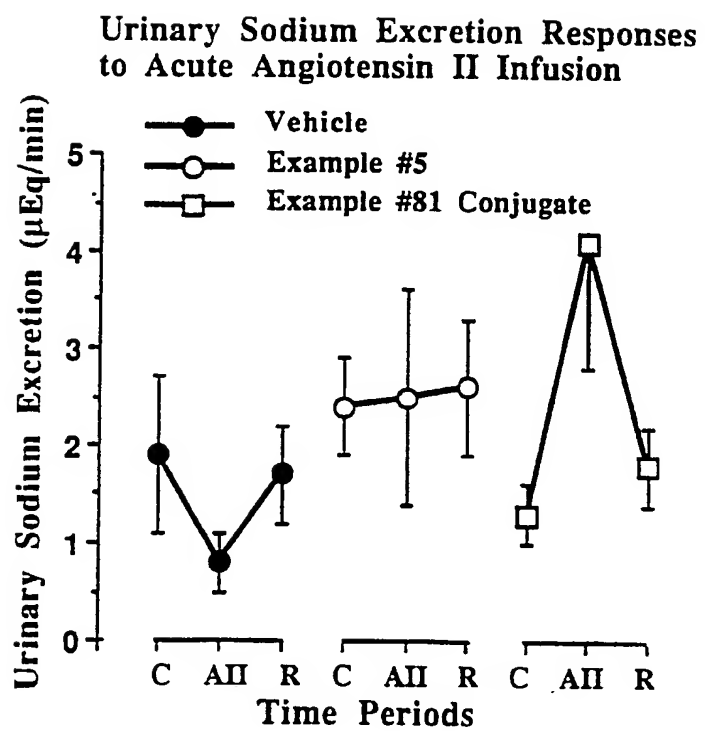


Figure 3

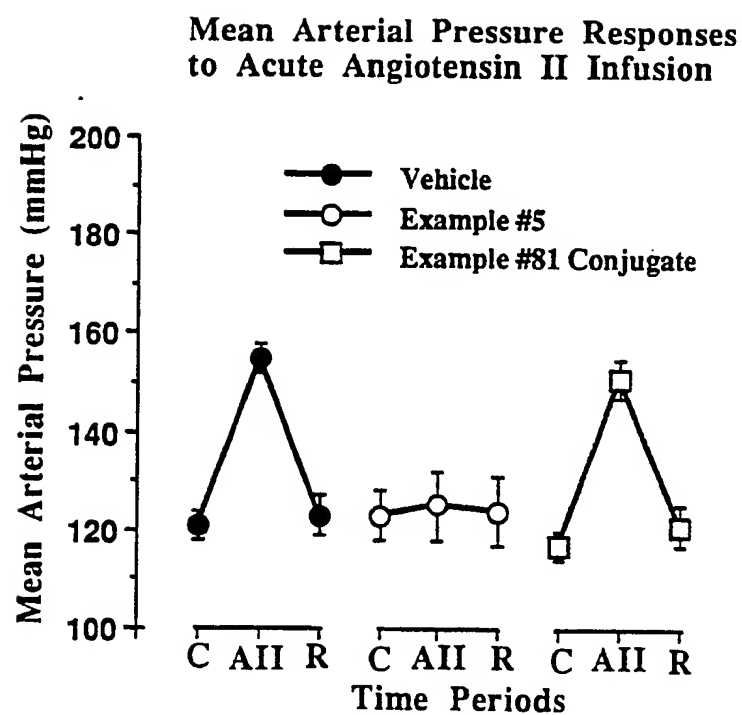


Figure 4

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